An epidemiological investigation into the incidence, prevalence, treatment and comorbidities associated with polymyalgia rheumatica in the United Kingdom 1990-2015

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Declaration

The idea for this study was conceived by myself, Sara Muller (SM), Christian Mallen (CM) and Alyshah Abdul Sultan (AAS) and Toby Helliwell (TH).

The study design for the incidence, case control and cohort studies was developed by myself with assistance from SM, CM, AAS and TH. Ethical approval for the study was obtained from the independent scientific advisory committee of the Medicines and Health RA. Management, analysis and interpretation of the data were performed by myself and AS.

Joanne Jordan (Research Information Manager, Keele University) and Opeyemi Babatunde (Research Associate: Systematic Reviews, Keele University) gave assistance with the development of protocol and search strategy for the systematic review. Literature search was performed by myself, while TH assisted me with title and full text review.

The word count of this thesis is 68,144. This excludes all the prefatory material, (Declaration, Funding, Acknowledgements, Abstract, Published papers from this thesis, Table of Contents, List of Tables, List of Figures, Content and organisation of this thesis and List of abbreviations used in this study) as well as the References and Appendices.

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I would also like to thank my wife Chloë and my children Oliver and Catherine for their love, patience and support during the lengthy study period.

This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone.

Abstract

Background

Polymyalgia rheumatica (PMR) is a common inflammatory rheumatic disease that affects older people. It can cause stiffness, severe pain and significant impairment to daily activities. Glucocorticoids (GCs) remain the mainstay of treatment. Contemporary estimates of the incidence and prevalence are lacking, and no previous study has assessed treatment patterns at a population level. Patients with a diagnosis of PMR may have an increased risk of comorbidities such as vascular disease or cancer, and the effect of PMR on mortality is uncertain.

Methods

This thesis contained results from a series of observational studies of PMR. The data sources included the Clinical Practice Research Datalink, Hospital Episode Statistics and Office of National Statistics Death registration datasets. A range of outcomes was assessed, including incidence, prevalence, treatment, comorbidities, hospital admissions and mortality.

Results

This study estimated that, in patients aged over 40 years, the prevalence and incidence of PMR in the UK was 0.85% and 95.9 per 100,000 respectively. Median (IQR) continuous glucocorticoid (GC) treatment duration was 15.8 (7.9,

31.2) months. However, around 25% of patients received more than four years total therapy. Patients with a diagnosis of PMR had a greater burden of comorbid disease compared to matched controls, and were more likely to be diagnosed with vascular, respiratory, renal, autoimmune, endocrine and psychiatric diseases. However, they were less likely to be diagnosed with cancer or dementia. Despite these differences, PMR had a neutral effect on all-cause mortality.

Conclusions

PMR is a common inflammatory rheumatological disease, affecting 1 in 120 adults aged over 40 years. Incidence is stable. Management of PMR largely followed guidelines, but there was a subset of patients subject to prolonged GC therapy. Although, compared to matched controls, patients with PMR have a slightly different profile of comorbid disease, no difference in mortality was observed.

Published papers from this thesis

Partington, Richard, Toby Helliwell, Sara Muller, Alyshah Abdul Sultan, Christian Mallen, Alyshah Abdul Sultan, and Christian Mallen. 2018. “Comorbidities in Polymyalgia Rheumatica: A Systematic Review.” *Arthritis Research & Therapy* 20 (1). Arthritis Research & Therapy: 258. doi:10.1186/s13075-018-1757-y.

Partington, Richard James, Sara Muller, Toby Helliwell, Christian D Mallen, and Alyshah Abdul Sultan. 2018. “Incidence, Prevalence and Treatment Burden of Polymyalgia Rheumatica in the UK over Two Decades: A Population-Based Study.” *Annals of the Rheumatic Diseases* 77 (12): 1750–56. doi:10.1136/annrheumdis-2018-213883.

Muller, Sara, Samantha Hider, Toby Helliwell, Richard Partington, and Christian D Mallen. 2018. “The Real Evidence for Polymyalgia Rheumatica as a Paraneoplastic Syndrome.” *Rheumatismo* 70 (1): 23–24. doi:10.4081/jlimnol.2014.817.

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Context and organisation of this thesis

In 2013 I completed my General Practice Vocational Training scheme and decided to try and find a role in primary care research.

My first foray into academia was a position as a Clinical Teaching Fellow at Lancaster University. This job came with responsibilities such as the creation of teaching materials, written exam questions and objective structured clinical examination scenarios. Alongside this, my responsibilities included setting and marking special study modules. While this occupied part of my time, I continued to work as a salaried General Practitioner and concurrently undertook a two year part time taught MSc in Clinical Pharmacology and Therapeutics at Glasgow University.

The experience and knowledge I gained from these roles enabled me to be successful in my application for a role as a Clinical Research Fellow at Keele University, which I commenced in August 2016. I chose this PhD topic as it fitted perfectly with my research interests of primary care, epidemiology, prescribing and musculoskeletal medicine. Furthermore, in my role as a GP, I have observed the effects of prolonged glucocorticoid prescribing and I was privileged to be able to dedicate time to investigate the treatment burden for which PMR is responsible.

My thesis is organised as follows:

Chapter 1:

Introduction to the disease polymyalgia rheumatica and review of existing estimates of incidence and prevalence of polymyalgia rheumatica.

This is an explanation of what PMR is and describes the history of the illness and current estimates of the epidemiology of the condition.

Chapter 2:

Clinical Practice Research Datalink.

An introduction to the clinical dataset used, with comparison to the UK population to assess whether it is representative.

Chapter 3:

The incidence and prevalence of polymyalgia rheumatica in the United Kingdom over two decades: a population-based study.

The number of new and existing diagnoses of PMR in the UK over two decades.

Chapter 4

The treatment burden of polymyalgia rheumatica in the United Kingdom over two decades: a population-based study.

Details of glucocorticoid prescriptions made to patients with a diagnosis of PMR.

Chapter 5:

Comorbidities in polymyalgia rheumatica: a systematic review.

A systematic review of existing literature looking into whether comorbidities are present more often in patients with PMR either at the time of diagnosis or prospectively following.

Chapter 6:

Comorbidities and polymyalgia rheumatica: a population based case control and cohort study.

A study investigating whether comorbidities, which were identified following systematic review and expert input, are more or less likely to be present either before or after diagnosis of PMR.

Chapter 7:

Comorbidities and polymyalgia rheumatica, mortality data and hospital admissions.

A comprehensive study into the health of patients with PMR compared to matched controls using datasets containing hospital admission and discharge data as well as mortality statistics.

Chapter 8:

Discussion.

List of abbreviations used in this thesis

asd- as directed

CCF- Congestive cardiac failure

COPD- Chronic obstructive pulmonary disease

CPRD- Clinical Practice Research Datalink

CQC- Care Quality Commission

crd- Current registration date

CRP- C-reactive protein

CVA- Cerebrovascular disease

CVD- Cardiovascular disease

DM- Diabetes Mellitus

DMARD- disease modifying anti-rheumatic drugs

DoH- Department of Health

EHR- Electronic Healthcare Record

EMIS- Egton Medical Information Systems

EORA- Elderly-onset rheumatoid arthritis

ESR- Erythrocyte sedimentation rate

EU- European Union

frd- First registration date

GC- Glucocorticoid

GCA- Giant cell arteritis

GDPR- General Data Protection Regulation

GP- General Practitioner

HCL- Hairy cell leukaemia

HES- Hospital Episode Statistics

HL- Hodgkin's lymphoma

HLA- Human leucocyte antigen

HR- Hazard ratio

HTN- Hypertension

ICD 10- International statistical classification of diseases and related health problems 10th revision

IRR- Incidence rate ratio

lcd- Last collection date

LL- Leukaemia, lymphoma

LRTI- Lower respiratory tract infection

MeSH- Medical Subject Headings

MGUS- Monoclonal gammopathy of undetermined significance

MHRA- Medicines and Healthcare products Regulatory Agency

MPN- Myeloproliferative neoplasm

NICE- National Institute for Health and Care Excellence

NIHR- National Institute for Health Research

NHL- Non Hodgkin's lymphoma

NHS- National Health Service

NLM- National Library of Medicine

OA- Osteoarthritis

ONS- Office for National Statistics

OR- Odds ratio

PMR- Polymyalgia rheumatica

PV- Plasma viscosity

PVD- Peripheral vascular disease

QoF- Quality and Outcomes Framework

RA- Rheumatoid arthritis

RCT- Randomised control trial

SLE- Systemic lupus erythematosus

T1DM- Type one diabetes mellitus

T2DM- Type two diabetes mellitus

tod- Transfer out date

THIN- The Health Improvement Network

TRUD- NHS Technology Reference Data Update Distribution

UC- Ulcerative colitis

URTI- Upper respiratory tract infection

UTI- Urinary tract infection

UK- United Kingdom

uts- Up-to-standard date

Chapter 1 INTRODUCTION

1.1 Introduction to thesis

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease affecting people over the age of 50 and is most commonly seen in people of Northern European origin. (Michet and Matteson, 2008) Its impact on patients' lives can be devastating if not treated, causing stiffness, severe pain, systemic illness and significant impairment to daily activities. (Helliwell et al., 2016) The aims of this thesis were to study the incidence, prevalence and management of, as well as the comorbidities associated with, PMR. These aims were met using a national database of primary care health records: the Clinical Practice Data Link (CPRD)

This chapter provides an introduction to PMR, including the aetiology, pathophysiology, history, clinical features, investigations into, and management of, PMR. Finally, existing estimates of the incidence and prevalence of PMR will be described.

1.2 Aetiology

The cause of PMR is unknown, however studies suggest epidemiological and genetic factors may play a role. Familial aggregation of PMR, although rare, has been described. (Liozon and Ouattara, 2009) Complicating the problem of ascertaining the cause of PMR is the significant, and well documented, crossover between PMR and Giant Cell Arteritis (GCA). GCA is a chronic, systemic

vasculitis affecting large and medium sized arteries, (Borchers and Gershwin, 2012) which classically presents with a new onset headache over the temporal or occipital areas; although it may localise elsewhere. (Salvarani, Cantini and Hunder, 2008) Around 40-60% of patients with GCA have symptoms of PMR at diagnosis, while 16-21% of patients with PMR will develop GCA during their disease course. (Salvarani, Cantini and Hunder, 2008)

A number of studies have reported an association between PMR and certain genetic polymorphisms. These polymorphisms have been found in an area of the genome responsible for the coding of transcription factors of specific immune components involved in immune regulation. (Gonzalez-Gay et al., 1999) Alterations in this part of the genome lead to alterations in the expression of genes for interleukin 6, interleukin 1 receptor antagonist and intracellular adhesion molecule 1, and have been found to be associated with an increased risk of PMR disease onset or severity. (González-Gay et al., 2003; Boiardi et al., 2006; Alvarez-Rodriguez et al., 2009) More recently, genetic associations between specific human leucocyte antigen-DR (HLA-DR) genotypes and GCA have been found, (Carmona et al., 2015) although the relationship of these molecules to PMR remains unclear. (González-Gay, Matteson and Castañeda, 2017) So far it has not been possible to elucidate whether there are genetic, viral or cytokine features common to both conditions. (Cantini et al., 2004)

Many of the studies which have assessed the degree to which genetics is responsible for PMR have only been able to utilise small (n<150) cohorts of patients and frequently use patients with a diagnosis of both PMR and GCA. This

has so far diluted their ability to isolate specific polymorphisms which could be implicated in the development of pure PMR.

1.3 Pathophysiology

PMR is an inflammatory rheumatological disease. Key laboratory features of the disease are an elevation in acute phase proteins, such as CRP (C-reactive protein), PV (plasma viscosity), fibrinogen and ESR (erythrocyte sedimentation rate). (Dasgupta et al., 2012; McCarthy et al., 2013) Acute phase reactants are produced in the body in response to acute injury, infection, or other forms of inflammation. Medically, they can be used to identify when inflammation is present in the body and, by the magnitude of their elevation, the extent of the inflammation. (Ballantyne and Nambi, 2005)

The location of the inflammation in PMR appears to be articular or periarticular. Imaging studies utilising a mixture of modalities, including ultrasound, magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (PET) scans, have demonstrated bursitis (inflammation of the bursa) around the shoulder, hips and cervical spine (Salvarani et al., 1997, 2013; Frediani et al., 2002; Blockmans et al., 2007) as well as synovitis (inflammation of the inner joint capsule) in the shoulders and hips. (Koski, 1992; Frediani et al., 2002)

Histological analyses of tissue samples (for example, synovial membranes) taken from people with PMR generally show infiltration with macrophages and CD4 T-cells on a background of chronic inflammation. (Meliconi et al., 1996) These cells, particularly macrophages, synthesise molecules such as interleukin 1 and 6

which, as previously discussed, are known to be increased in patients with PMR. (Dasgupta and Panayi 1990) Intriguingly, although myalgia is a cardinal symptom of PMR, muscle inflammation is not typically found. The presence of inflammation on muscle biopsy is indicative of polymyositis, a rare autoimmune disease causing proximal weakness, with raised muscle enzymes, and associations with interstitial lung disease. (Hopkinson, Shawe and Gumpel, 1991; Clark and Isenberg, 2018)

Whether PMR can be regarded as an autoimmune (AD) or auto-inflammatory disease (AID) is also the subject of debate. (Floris et al., 2018) Autoimmune and auto-inflammatory diseases are regarded as opposite ends of an immunological disease spectrum. An auto-inflammatory disease involves aberrant activation of the innate immune system without autoantibody production or T lymphocyte activation. In comparison, autoimmune diseases involve an abnormal activation of the adaptive immune system. (Doria et al., 2012) PMR doesn't easily fit in either end of this spectrum. For example, it has some characteristics in favour of classification as an auto-inflammatory disease such as the lack of specific autoantibodies; (Floris et al., 2018) however, in common with autoimmune diseases, PMR is strongly associated with female sex. (Smeeth, Cook and Hall, 2006) Currently, the overall consensus is that PMR has more in common with auto-inflammatory rather than autoimmune diseases. (Floris et al., 2018)

GCA, in contrast, is a chronic, idiopathic granulomatous vasculitis of the medium and large arteries. (Lensen et al., 2016) GCA is categorised as a systemic connective tissue disease, (World Health Organisation, 2016) within this group are other autoimmune conditions, such as systemic lupus erythematosus (SLE),

systemic sclerosis and dermatopolymyositis. GCA has previously been known by a number of names, for example temporal arteritis. Although this name implies the condition exclusively affects the temporal artery, many patients are also found to have vasculitis of a number of large vessels, including the aorta, subclavian and vertebral arteries. (Bossert et al., 2011) Furthermore, the degree of inflammation can vary from florid accumulations of giant cells, to intermittent areas of non-granulomatous inflammation interspersed with normal vessel walls ('skip lesions'). Giant cells are multinucleated masses produced by the fusion of many cells that can form granulomas, which are organised collections of epithelioid cells. (Stacy, Rizzo and Cestari, 2011)

The clinical and laboratory findings in PMR share a number of features with GCA, such as female predominance, chronically raised levels of inflammation, specifically interleukin 6, (Weyand et al., 2000; Alvarez-Rodríguez et al., 2010) as well as a pronounced response to glucocorticoid (GC) therapy. Furthermore, it has been found that in patients with PMR, even without clinical features of GCA, temporal artery biopsies may show evidence of subclinical inflammation. (Weyand et al., 1994; Weyand and Goronzy, 2003)

PMR and GCA are therefore chronic inflammatory conditions that commonly coexist. Laboratory findings of raised inflammation occur in both diseases and immunosuppressant therapy, in the form of glucocorticoids, work well in both diseases. However, the site of inflammation in each condition, and their pathophysiology, differ significantly. In spite of these differences, both of these conditions, and the link between them, were tentatively identified before the development of sophisticated laboratory tests or treatments.

1.4 History of Polymyalgia Rheumatica

Polymyalgia rheumatica was first described in medical literature in 1888 by Dr William Bruce. (Bruce, 1888) In this paper, five patients, who were all men, were described; each of them had severe muscle pain or stiffness after a period of exposure to cold temperatures. Four had shoulder girdle involvement, and in two there was peripheral joint swelling. Each patient exhibited a complete recovery over a period of up to two years, although some relapses were observed.

True recovery from inflammatory rheumatological conditions was at the time unheralded due to the paucity of treatment options. The improvement of these patients was the more remarkable in view of their age, all were at least 60 and four were over 70 years. This, in part, helped Bruce reach the conclusion that he had found a novel condition. (Mowat, 1981) The name given to this ailment was senile rheumatic gout.

This unusual collection of cases was found at a spa at Strathpeffer, 24 miles north-west of Inverness in the United Kingdom. Taking baths in natural springs in an attempt to cure medical ailments had been practised since ancient Greece. Bathing was recommended by physicians of the classical era such as Hippocrates, Asclepiades, Pliny the Elder and Galen. (van Tubergen and van der Linden, 2002) This practice, however, fell out of favour through the Dark and Middle Ages. From the Renaissance, and particularly the beginning of the 19th century, interest in bathing in natural springs as a treatment began to grow. Around the Victorian era, and for decades after, bathing in springs was recommended for many rheumatic diseases, although this was largely due to the absence of effective medical treatments. This meant an unusual concentration of

rarer rheumatological conditions could be found in spa towns, sometimes allowing identification and classification of new conditions. (Bird, 2008)

After Bruce, no further observations about PMR were recorded until almost halfway through the twentieth century. Over a period of around twenty years, numerous studies were published with descriptions of patients with PMR and multiple attempts were made to name the condition and understand its pathophysiology. In 1945 Meulengracht described two patients with shoulder pain and stiffness and constitutional symptoms including fever and weight loss as well as a raised Erythrocyte Sedimentation Rate (ESR). Their symptoms gradually improved and the patients recovered. He proposed the term periarthrosis humeroscapularis. (Meulengracht E, 1945)

Also, in 1945, Holst and Johansen reported a case series of 5 women who suffered limitation in shoulder movement alongside pain in the shoulders, arms and hips with an elevated ESR. Two of the patients had slight joint swelling and low grade fevers were noted in three patients. These symptoms and signs regressed after a year. At this time, the name given to the condition was peri-extraarticular rheumatism. (Holst and Johansen, 1945)

A presentation was made at the second European Congress of Rheumatology in Barcelona in 1951. In this presentation, the cases of 13 patients with the characteristic pattern of girdle pain and stiffness, raised inflammatory markers and subsequent regression of symptoms were discussed. (Kersley GD, 1951) The name chosen for the disorder at that point was myalgic syndrome of the aged with systemic reaction. This presentation also discussed the first use of

glucocorticoids as treatment for the condition and investigation findings, such as negative muscle biopsies.

Later, in 1953, Forestier and Certonciny published observations of 25 patients seen in France aged between 45 and 79 who presented with pain in the shoulder and hip girdles, systemic symptoms and a raised ESR. (Forestier and Certonciny, 1953) They noted there was no sign of joint swelling and that the symptoms resolved over a period of months. The name suggested in this case was pseudo-polyarthrite rhizomélique.

In the same year a larger cohort of 50 patients were discussed in detail by Bagratuni; each of them had developed what he termed anarthritic rheumatoid syndrome, and most improved with time, with only two progressing to frank rheumatoid arthritis. (Bagratuni, 1963)

Finally, in 1957, Barber, a physician from Buxton in the United Kingdom (UK), described 12 patients with stiffness and pain, and noted further that the stiffness often occurred in the morning. He suggested the condition be named polymyalgia rheumatica. (Barber, 1957) Buxton, like Strathpeffer, is a spa town in the UK, and so it can be seen that even well into the twentieth century, rheumatology retained strong roots in these areas.

Subsequently, editorials published in the British Medical Journal in 1957 (BMJ, 1957) and the Lancet in 1961 (Lancet, 1961) increased general awareness of this condition and cemented the term polymyalgia rheumatica in the medical literature. It has been postulated that the reason PMR has been identified only relatively recently is simply that it is a disease of old age, and it is only in recent human history that life expectancy has lengthened to the extent that significant

numbers of patients are alive for sufficient time to develop PMR. (Dequeker, 1981)

1.5 History of PMR and GCA

The identification of the link between GCA and PMR occurred around the same time as awareness of PMR was increasing. The first time the similarity between the symptoms of PMR and GCA was highlighted was during the second European Congress of Rheumatology in 1951. (Porsman, 1951) Following this, in 1960, Paulley and Hughes published a series of 71 patients with GCA. They noted 32 patients had symptoms of PMR and speculated whether PMR may be a symptom of GCA. (Paulley et al., 1960)

In 1963, Alestig and Barr took temporal artery biopsies in patients with PMR who did not have temporal symptoms typical of GCA. Despite the fact that these patients did not have symptoms or signs of GCA, 7 of the sample of 10 had biopsies positive for arteritis. These findings were replicated in a study by Hamrin in 1964. (Hamrin, Jonsson and Landberg, 1964) By 1970 the link between PMR and GCA was well established in the medical literature, and the overall rate of positive temporal artery biopsy in PMR was thought to be around 10-20%. (Hunder, Disney and Ward, 1969)

However, GCA as a condition was recognised long before PMR; in fact human records of people with GCA predate all medical literature.

1.6 History of Giant Cell Arteritis

The first evidence of GCA may have inadvertently been recorded in artworks dating from Antiquity. A carving found on the Egyptian tomb of Pa-Aton-Em-Eb, which was produced around 1350BC, shows a harpist with a prominent temporal artery as well as a closed eye, indicating potential blindness, who appears to be staring into space. (Appelboom T, 1990)

Figure 1-1: Limestone scene from the Tomb Chapel of Paätenemheb, Sakkara. 1333-1307 B.C.

Around two thousand years later, in 1000 AD, a well-known mediaeval ophthalmologist, in what is now modern Iraq, named Ali ibn Isa al-Kahhal, first recognised a relationship between an inflamed temporal artery, headache and

visual symptoms, and suggested excision of the artery as a potential treatment. (Hollenhorst et al., 1960)

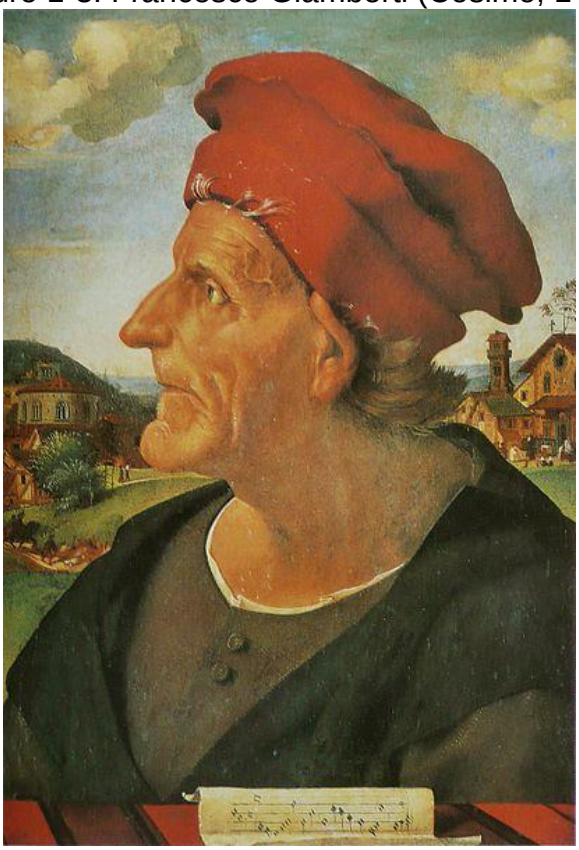
However, in Europe, the only evidence of GCA continued to be created by artists rather than recorded by physicians. For example, the painting below, which is now held in Bruges, of Canon Van der Paele and the Holy Virgin by Jan Van Eyck in 1436.

Figure 1-2: Canon Van der Paele and the Holy Virgin (Eyck, 1434)

In this painting it was observed that Canon Van der Paele had a prominent left temporal artery, loss of hair anterior to the ear on the same side and swelling of the left hand suggestive of peripheral oedema which can be associated with GCA. (Dequeker, 1981)

Another example of likely GCA in Renaissance art can be seen in Piero di Cosimo's 1505 portrait of Francesco Giamberti, which now hangs in Rijksmuseum, Amsterdam. In this, one of the typical signs of GCA, a torturous, inflamed temporal artery is again present. (Roth, 1969)

Figure 1-3: Francesco Giamberti (Cosimo, 1485)



In western medical literature, the first clinical description of GCA is credited to Jonathan Hutchinson who, in 1890, described a case of a gentleman who was almost 80 years of age with swollen and painful superficial temporal arteries. (Hutchinson, 1890)

More than 40 years later, Horton published two cases of patients with fever, weakness, anaemia and painful, tender areas along the temporal vessels.

Included in the study were biopsy samples demonstrating inflammation. (Horton, Magath and Brown, 1932) Soon after, in 1934, the two cases were revisited and the symptoms of headache and jaw claudication were added to the description. (Horton, Magath and Brown, 1934) Following this, in 1937, Horton and Magath described a further series of patients aged between 55 and 75 years with headache, jaw ache, tender temporal arteries and fever. Biopsy of the temporal artery revealed an arteritis. Much later, Horton published examples of experiments carried out that ruled out an infectious aetiology, leading to the conclusion that GCA was an autoimmune condition. (Horton, 1979) Many of the early case series of patients with GCA included descriptions of musculoskeletal pain, (Horton, Magath and Brown, 1934; Gilmour, 1941) however, no specific link was made between PMR and GCA.

The name given to describe this condition went through several iterations; initially Hutchison named it thrombotic arteritis of the aged. Horton used the term temporal arteritis; Kilbourne and Wolff then suggested cranial arteritis, as the temporal artery is not the only vessel involved. Others (Andersen, 1947; Schmidt, 1995) advocated naming the condition Horton's disease in homage to the person who first described it. However, the most common term now used to describe the condition, suggested by Gilmour, (Gilmour, 1941) is giant cell arteritis (GCA). This name arose because characteristically giant cells are found in temporal artery biopsies taken from patients with this condition. However, the nomenclature remains imperfect because, as discussed earlier, giant cells are only demonstrated in 50% or fewer of the histological samples taken from patients with GCA. (Murchison et al., 2012; Saedon et al., 2012)

GCA and PMR were therefore fully identified, defined and named as distinct clinical entities in medical literature, around 80 and 60 years ago respectively. In the years following this, knowledge of both conditions has increased and diagnostic processes have been refined in order to improve the reliability of identification and classification of patients who present with features suggestive of these conditions.

1.7 Clinical features and diagnosis of PMR

Clinically, most patients with PMR present to healthcare practitioners with acute or subacute onset of bilateral shoulder pain and stiffness. (Salvarani et al., 2002b; Salvarani, Cantini and Hunder, 2008) Other common symptoms include pain and stiffness in the upper arms, neck and hip girdle. This pain and stiffness often make completion of activities of daily living a challenge for patients, for example combing their hair or rising from a bed. (Mackie et al., 2015) This can also complicate the diagnostic process for clinicians as it may erroneously give the impression of muscle weakness, which is not typically a feature of PMR. (Michet and Matteson, 2008)

Alongside these local symptoms and signs, PMR is associated with systemic features in up to 40% of patients. These include a low grade fever, depression, fatigue, anorexia and weight loss. (Chuang et al., 1982; Salvarani et al., 1987) Furthermore, in some cases of PMR, a mild synovitis in the shoulder and hip joints has been observed. (Koski, 1992; Frediani et al., 2002)

PMR is very rare in patients aged less than 50 years old. Its incidence increases with age and it has a mean age of onset of around 73 years. (Doran et al., 2002) The diagnosis of PMR is clinical and is made when a patient has a combination of the characteristic cluster of symptoms and laboratory tests showing raised inflammatory markers (invariably ESR or CRP). (Helliwell et al., 2018) As previously discussed, no specific autoantibody has been identified as occurring with PMR to aid in diagnosis, (Floris et al., 2018) nor does it have any other specific diagnostic clinical feature or laboratory test.

This reliance on the clinical signs, and lack of a specific diagnostic marker, means the process of diagnosing a patient with PMR is somewhat more complex than otherwise anticipated. In the UK, most patients (71-84%) with PMR are diagnosed and managed in primary care. (Barraclough et al., 2008; Yates et al., 2016) However, a recent survey of UK General Practitioners (GPs), found that many found making a diagnosis of PMR challenging. A number of different reasons were given for this, but two main themes predominated. The first was in cases where patients presented atypically, for example patients with a classical history but normal inflammatory markers. The second theme was around non-specific presentations together with the wide range of differential diagnoses that are to be considered alongside PMR, compounded by the fact that multimorbidity is common among patients of the age group affected by PMR. (Helliwell et al., 2018)

In the absence of a specific diagnostic test, a number of clinical classification criteria have been created with the aim of increasing uniformity of diagnosis. The first to formally set criteria for PMR research was H A Bird et al. in 1979, followed

by Jones and Hazleman (1981) and Chuang et al. (1982). A review of these criteria, published in 2005, suggested that the Bird and Chuang criteria had the greatest sensitivity in correctly classifying PMR. However, its authors also made clear that their results could be better described as a "*test of homogeneity"* and that their results may be *"biased towards the study of "true" PMR rather than a clinical syndrome that might appear indistinguishable initially."* (Bird et al., 2005)

Following this review, a collaborative working group was formed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) to develop standardised classification criteria for PMR research. These criteria were published in 2012. (Dasgupta et al., 2012)

The first limitation of these criteria is apparent in their name. Clinical classification criteria exist primarily to create well-defined, relatively homogenous cohorts for clinical research. (Aggarwal et al., 2016) This is compared to diagnostic criteria which are for use in routine clinical care to guide diagnosis of individual patients. (Aggarwal et al., 2016) Therefore, it is not recommended to use clinical classification criteria in day to day healthcare practice.

The criteria are mainly based on clinical and simple laboratory findings, however they can also accommodate results from ultrasound imaging (table 1-1).

Table 1-1: Clinical classification criteria for PMR

Criteria	Points
Clinical	
Morning stiffness duration >45 minutes	2
Hip pain or limited range of motion	1
Absence of RF* or ACPA*	2
Absence of other joint pain	1
Threshold for PMR classification >3 points	/ 6
Ultrasound	
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	1
If ultrasound results included, threshold for PMR > 4 points	/ 8

*RF (Rheumatoid factor) ACPA (anticitrullinated protein antibody)

Adapted from: Dasgupta B, Cimmino MA, Maradit-Kremers H, et al 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative Annals of the Rheumatic Diseases 2012;71:484-492 (Dasgupta et al., 2012)

These criteria reflect the typical symptoms of a patient with suspected PMR very well, and their sensitivity can be further enhanced through the use of ultrasound imaging, where available. Furthermore, by excluding patients with rheumatoid factor, there is a specific aim to reduce misdiagnosis of patients with rheumatoid arthritis, (RA) which can present with a polymyalgic onset.

Rheumatoid arthritis is a chronic inflammatory disease which can cause cartilage and bone damage that classically presents with subacute onset of tender, swollen joints with morning stiffness and raised inflammatory markers. (Smolen, Aletaha and McInnes, 2016) Therefore RA is regarded as the prime differential diagnosis in patients with PMR, particularly in the presence of peripheral synovitis. (Cutolo, Cimmino and Sulli, 2009) The difficulty in differentiating between PMR and RA is compounded by the fact that both are particularly

responsive to treatment with glucocorticoids (GCs). A full list of differential diagnoses to consider with PMR is below (table 1-2).

Table 1-2: Differential diagnosis of PMR

Rheumatological diseases	Rheumatoid arthritis
	Spondyloarthropathy
	Crystalline arthritis (calcium pyrophosphate disease and calcium hydroxyapatite disorders)
	Remitting seronegative symmetric synovitis with pitting oedema syndrome
	Connective tissue diseases
	Vasculitis (giant cell arteritis, antineutrophil cytoplasmic antibody-associated vasculitis)
	Inflammatory myopathies (dermatomyositis, polymyositis)
Non-inflammatory musculoskeletal disorders	Rotator-cuff disease
	Adhesive capsulitis
	Degenerative joint disease
	Fibromyalgia
Endocrinopathies	Thyroid diseases
	Disorders of the parathyroid gland
Infections	Viral
	Bacterial sepsis, endocarditis, disc space infection, septic arthritis
	Mycobacterial—e.g. tuberculosis
Malignant diseases	Solid, haematological
Miscellaneous disorders	Parkinsonism
	Depression
	Hypovitaminosis D
	Drug-induced myopathy—e.g. from statins

Reproduced from Kermani T, Warrington KW. Polymyalgia rheumatica. The Lancet 2013; 381(9680), 63-72 (Kermani and Warrington, 2013)

The difficulty in making a diagnosis is therefore due to two main factors, a lack of a specific diagnostic test for PMR and a very long list of plausible, common, and medically serious, differential diagnoses. One of the most frequently diagnosed differentials, RA, tends to present between the ages of 40-60, but it can be diagnosed at any age. (Allen, Carville and McKenna, 2018) Elderly-onset

rheumatoid arthritis (EORA), which is defined as rheumatoid arthritis that develops in patients aged 60 or over, (Wakura et al., 2016) confuses the diagnostic process still further. EORA therefore presents therefore at a similar age to PMR and its early symptomatology mirrors PMR. Furthermore, despite the requirement to exclude RA in order to diagnose PMR, studies have reported that many patients with an initial diagnosis of PMR later go on to develop RA and other related conditions, such as systemic lupus erythematosus (SLE) and spondyloarthropathies. (Dasgupta et al. 2008)

The suggestion, implicit in the clinical classification criteria, that PMR and RA cannot coexist, is reinforced and extended in the most recent recommendations made by EULAR and ACR for the management of PMR. They suggest that prior to making a diagnosis of PMR, *"clinical evaluation should be directed towards exclusion of relevant mimicking conditions (e.g. non-inflammatory, inflammatory (such as giant cell arteritis or rheumatoid arthritis), drug-induced, endocrine, infective and neoplastic)".* (Dejaco, Singh, Perel, et al., 2015)

Therefore, the current recommended classification model defines PMR, perhaps inadvertently, as a diagnosis of exclusion. However, as previously discussed, PMR is a disease of older people. As such, patients with a diagnosis of PMR are as likely as others in this age group to have already developed, or go onto develop, one or more of these morbidities. The critical question then, is whether a diagnosis with one of these conditions should invalidate or supersede a diagnosis of PMR. To give an example, osteoarthritis, a condition which affects more than 40% of people aged over 80 years, (Litwic et al., 2013) is statistically likely to affect a large proportion of patients who have PMR. Should the presence

of osteoarthritis preclude a new, or rule out an existing, diagnosis of PMR? In order to answer these questions, it is necessary to define which comorbidities frequently coexist in patients with PMR.

1.8 Comorbidities in PMR

Comorbidities can be regarded, as per Feinstein's description, as, "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study." (Feinstein, 1970) There are three ways in which different diseases may be found in the same individual - chance, surveillance bias or causal association. (Valderas et al., 2009) For example, two common conditions may coexist due to chance, such as hypertension and asthma, simply because they are both very common. Surveillance bias may lead to comorbidities being diagnosed more often in patients with an index condition due to intensive follow up. (Haut and Pronovost, 2011) Finally, causation is where comorbidities are directly linked, for example a patient with hypertension who subsequently develops coronary artery disease, as the former is a risk for the latter.

Multimorbidity is commonly defined as when a patient has two or more chronic medical conditions. (Wallace et al., 2015) Aging is an important predictor of multimorbidity; a recent Scottish study found the number of adults with two or more chronic conditions increased from 30.4% between 45-64 years, to 64.9% in those aged 65 to 84 and greater than 80% in those aged over 85. (Barnett et al., 2012) Therefore, patients with PMR, for whom the mean age of onset is

around 73 years (Doran et al., 2002) are demographically highly likely to have at least one comorbidity. A study of newly diagnosed cancer patients in the United States found the most common comorbidities in patients aged 65-73 were hypertension, diabetes mellitus, respiratory disease, previous solid tumour(s) and angina. (Piccirillo et al., 2008) Each of these conditions had a prevalence of greater than 10%.

Therefore, some of the conditions which, according to current criteria, would preclude diagnosis of PMR are likely to be very common in the age group affected by PMR. The uncertainty around the general health of patients with PMR, and comorbidities that may coexist with it, present a challenge for healthcare practitioners who deal most with this condition, be they from primary or secondary care. (Helliwell et al., 2018) This lack of clarity around the diagnosis of PMR extends also to its management, which is considered in detail in the following section.

1.9 Management of PMR

PMR symptoms are effectively managed with gradually reducing glucocorticoid (GC) therapy, from moderate to low doses. (Buttgereit et al., 2016) Joint guidance released by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) affirms that PMR should be treated in this way and that GC treatment for most patients should end by two years, and prescribing should be individualised to ensure the minimum effective duration and dose is prescribed. (Dejaco, Singh, Perel, et al., 2015) Some risk factors for

relapse or prolonged therapy, have been suggested, such as female sex, (Cimmino et al., 2006) high ESR (Barraclough et al., 2008) and peripheral inflammatory arthritis. (Salvarani et al., 1998)

The initial GC dose to be prescribed is recommended to lie between 12.5mg and 25mg prednisolone equivalent per day. A higher dose can be considered if the patient is thought to be at higher risk of relapse or a lower dose in those with risk factors for GC related side effects. (Dejaco, Singh, Perel, et al., 2015)

Glucocorticoids are potent inhibitors of inflammatory processes. They act by either direct binding to glucocorticoid receptors or by interaction with transcription factors, and subsequently inhibit many molecules associated with inflammation, including cytokines, chemokines and arachidonic acid metabolites. (Van Der Velden, 1998)

The guidelines also recommended strongly against the use of non-steroidal anti-inflammatory drugs (NSAIDs) in PMR and do not make recommendations on the use of biologic treatments (which are commonly used in other rheumatological conditions) as trials into their effectiveness were ongoing at the time of publication. (Dejaco, Singh, Perel, et al., 2015) Two of these trials have published results subsequent to the guidelines being published. The first showed tocilizumab to be effective in a small (n=13) sample of patients with intractable PMR. (Izumi et al., 2015) However, the other trial (NCT01364389) was terminated early as the biologic agents were less effective in reducing disease activity than conventional GC therapy.

The majority of cases of PMR in the United Kingdom are diagnosed and managed in primary care (71-84%). (Barraclough et al., 2008; Yates et al., 2016)

Guidelines suggest referral to secondary care should be considered where there is uncertainty regarding diagnosis, either because of an atypical presentation, high risk of therapy related side effects, prolonged or inadequate response to therapy, or relapses following cessation of treatment. (Dejaco, Singh, Perel, et al., 2015)

Therefore, within the current guidelines, there is recognition that a proportion of patients experience symptom flare upon cessation, or even reduction, of GC therapy (a “symptom tail’). (Mackie et al., 2014) This has led to the suspicion that a significant number of patients are subject to GC treatment for more than two years following diagnosis. (Liew, Owen and Buchanan, 2018) Previous studies have shown that long-term GC treatment increases a person’s risk of a wide range of conditions, including hypertension, cardiovascular disease, type two diabetes, cataract, osteoporosis and proximal myopathy. (Oray et al., 2016)

Therefore, although much is known of the aetiology, pathophysiology, history, clinical characteristics, and diagnosis and management of PMR, significant gaps in the body of knowledge remain. In order to ascertain the clinical importance of these gaps it is important to first establish what the existing estimates are of how many people are affected by PMR.

1.10 Epidemiology of Polymyalgia Rheumatica

In this section, a summary of the development, and current estimates, of the incidence and prevalence of PMR is presented.

Epidemiology is defined as *"the study of the distribution and determinants of health related states or events (including disease), and the application of this study to the control of diseases and other health problems."* (World Health Organisation, 2017) In order to effectively allocate resources within a healthcare economy it is necessary to ascertain accurate estimates of the number of patients with different medical conditions. There are several ways to measure disease frequency, all of which must be related to the total population at risk of the disease.

Incidence is defined as *"the rate at which new cases occur in a population during a specified period"*. (British Medical Journal, 2017) When a population is stable, incidence is expressed as below: (Tenny and Boktor, 2018)

$$\frac{Number\ of\ new\ cases}{Total\ population\ at\ risk\ x\ timeframe} = Incidence\ (cases/persontime)$$

Point prevalence is the "*proportion of a population that are cases at a point in time".* Period prevalence is similar in that it measures the proportion of a population that has a disease but within a period of time, for example twelve months. (British Medical Journal, 2017) Therefore, this measure contrasts to incidence which measures only new cases within a specified period.

Incidence and prevalence are inter-related. Each incident case of a disease is a prevalent case also, until resolution of the disease. Therefore, in the case of a condition such as PMR which has a relatively long duration, and does not pose a direct threat to life, even relatively low incident rates can cause high prevalence figures. This effect has been summarised as:

$$Prevalence = Incidence\ x\ average\ duration\ of\ disease$$

Estimates have been calculated for both incidence and prevalence of PMR, and these will each be considered in turn.

1.11 Incidence of Polymyalgia Rheumatica

A number of studies have estimated the incidence of PMR to lie between 12 - 113 per 100,000 person years. (Salvarani et al., 1991; Barraclough et al., 2008; Raheel et al., 2017) However, despite many patients being treated in primary care, much of the existing literature is based on secondary care hospital records, therefore the burden of disease may have been underestimated. The studies investigating the incidence of PMR are summarised in table 1-3.

Table 1-3: Incidence of Polymyalgia Rheumatica

Authors	**Country**	**Population size**	**Study Type**	**Incidence rate per 100,000**
Barraclough et al. (2008)	United Kingdom, Gloucestershire	37,908	General Practice	113*
JT Gran and Myklebust (1997)	Norway, Aust Auger	97,314	Hospital	112.6*
Smeeth, Cook, and Hall (2006)	United Kingdom	17,830,028 [+]	Database	84**
Boesen and Sorensen (1987)	Denmark, Ribe	214,700	Survey	68.3*
Raheel et al. (2017)	United States, Olmsted County	109,555	Hospital	63.9*
Schaufelberger, Bengtsson, and Andersson (1995)	Goteborg, Sweden	435,000	Hospital	49.7
Elling, Olsson, and Elling (1997)	Denmark	10,818	Database	41.3
M A Gonzalez-Gay and Garcia-Porrua (1999)	Spain, Lugo	250,000	Hospital	18.67*
C Salvarani et al. (1991)	Italy, Reggio Emilia	169,950	Hospital	12.7*

*** = in patients > 50 years ** = in patients > 40 years [+] = total person years**

The study with the largest sample size was from the UK by Smeeth, Cook, and Hall 2006. In this study they used the primary care database that was also used in this thesis, albeit an earlier version. Therefore, this study was a key comparator for the findings of this thesis, however the final year of data this study reported was 2001. They found one of the highest estimates of incidence rate of PMR compared to other studies, as well as a gradual trend towards an increase in the incidence rate over time. This study also found that the incidence rates in the UK were higher in the south of the UK compared to the north. This finding is the reverse of worldwide trends where the incidence of PMR has been found to increase at higher latitudes; with the lowest estimates of PMR incidence being found around in Southern Europe. (Carlo Salvarani et al., 1995; Gonzalez-Gay et al., 1999, 2009; Herlyn et al., 2014; Buttgereit et al., 2016)

The study that found the highest incidence rate, 113 per 100,000 patients, was a study based in primary care from the south of England. (Hayward et al., 2014) This finding is consistent with Smeeth, Cook, and Hall 2006 who reported that there was a higher incidence in the south of England and Hayward et al's study was also based in primary care. However, although the sample size is large, (n=37,908) the relative rarity of PMR meant that only 183 new diagnoses of PMR were seen over a ten-year study period. The rate reported in this paper was similar to that found in a study from Norway by Gran et al. 1997. This study was based in secondary care but also made a concerted effort to identify patients in primary care also.

The most recent estimate of PMR incidence was reported to be 63.9 per 100,000 by Raheel et al. This study was the latest report from the Olmsted County cohort

of the Rochester Epidemiology Project. This is a long term project where epidemiological research has been carried out since 1966 on a population of people with linked healthcare records between all medical providers in a county in the United States. (St Sauver, Grossardt, Yawn, et al., 2012) The studied population has strong historic and genetic links to Northern European, and particularly Scandinavian, populations that may lead to higher incidences of PMR being found than might be expected.

This project, in the duration of follow up and completeness of medical record linkage has many strengths. However, it has been suggested that the sample size may be too small to adequately characterise relatively infrequent conditions and that the ethnic and socio-economic characteristics of the population may mean that some racial and ethnic groups are under-represented. (St Sauver, Grossardt, Leibson, et al., 2012)

In each of the incidence studies, where specifically reported, a strong association with PMR is found with increasing age and female sex, with a median age of diagnosis of between 70-75 years and a ratio of roughly two women developing PMR for every male. (Smeeth, Cook and Hall, 2006; Barraclough et al., 2008) This association between PMR and women is in contrast to the original description of PMR from 1888 (Bruce, 1888) where the case series consisted of five men.

1.12 Prevalence of Polymyalgia Rheumatica

Existing research estimates the prevalence of PMR to lie between 0.1-2.3%. The denominator used in the prevalence estimates given vary but, as PMR affects older people more often, usually excludes patients aged either under 50 or 55 years of age. In all but one study the prevalence was 1% or less (table 1-4). (C Salvarani et al., 1995; Eaton et al., 2010; Hayward et al., 2014)

Table 1-4 Prevalence of Polymyalgia Rheumatica

Authors	**Country**	**Population size**	**Study Type**	**Prevalence (%)**
Yates et al. (2016)	United Kingdom, East Anglia	5,108	GP, survey	2.27*
Hayward et al. (2014)	United Kingdom, North Staffordshire	13,831	GP, survey	1%**
Bernatsky et al. (2009)	Canada, Manitoba	1,100,000	Population	Urban: 0.6 Rural: 0.9
Doran et al. (2002)	United States, Olmsted County	124,919	Hospital	0.7
Manzo et al. (2009)	Italy, Massa Lubrense	12,186	GP survey	0.6**
C Salvarani et al. (1995)	United States, Olmsted County	109,555	Hospital	0.6**
Eaton et al. (2010)	Denmark	5,506,574	Population	0.3
Barrier, Billaud, and Magadur (1992)	France, Loire Atlantique	1,026,000	Survey	0.1
Boesen and Sorensen (1987)	Denmark, Ribe	214,700	Survey	0.1**
*** = patients >55 years ** = in patients > 50 years;**				

The highest prevalence was reported by a study based in primary care in the United Kingdom. (Yates et al., 2016) It was based on a small sample of patients (n=5,108) registered with a General Practice in East Anglia, in the south of the

UK, which corresponds with Smeeth et al's findings that PMR is more common in the south of the United Kingdom. (Smeeth, Cook and Hall, 2006)

The second highest prevalence was found in another study from the UK but again had a relatively small (n=13,831) sample size. (Hayward et al., 2014) This study reported prevalence over a four-year period. It was based upon the results of questionnaires sent to patients at eight general practices. Potential diagnoses were corroborated by cross referencing with medical records to ensure that each patient had at least two prednisolone prescriptions issued. Survey response rate was reasonably high (69.3%) and checking for GC therapy provided reassurance in the accuracy of the PMR diagnosis. However, just over 30% of patients did not respond to the questionnaire. These patients may not have responded if they felt the issues the questionnaire addressed didn't directly affect them, which could cause an overestimate of disease burden. Alternatively, if they had been too unwell to complete the questionnaire, this may lead to an underestimate.

The other weakness with this study is it took place within a relatively small and culturally homogenous region of the UK. Studies which are based in relatively small regions are prone to generalisability issues when attempting to apply the results to a wider population. For example, in Staffordshire, where this study took place, the population is different when compared to the rest of the UK, being slightly older, less ethnically diverse and with lower education levels. (Office for National Statistics, 2011) A nationwide study would provide a more accurate estimation of prevalence but would be more time consuming and cost significantly more.

A number of studies from Canada, (Bernatsky et al., 2009) Italy (Manzo et al., 2009) and the United States (C Salvarani et al., 1995; Doran et al., 2002) reported the prevalence of PMR to be between 0.6-0.9%. Of these, the prevalence of 0.6% reported by (Manzo et al., 2009) is perhaps the most surprising given the known predilection of PMR to affect northern, rather than southern, Europeans. This could be explained by the study design in which GPs were directly questioned, rather than only assessing medical records which would provide a more accurate estimate of disease burden in this region.

The next highest prevalence was found in Manitoba, a province in Canada. (Bernatsky et al., 2009) This study used hospitalisation databases and physician billing as the data source and also found a notable difference between the rural and urban prevalence of PMR (0.9 to 0.6%). This could provoke debate as to whether there is an environmental or socio-economic aetiology.

Of the three studies reporting the lowest prevalence estimates, two were published more than 25 years ago. (Boesen and Sorensen, 1987; Barrier, Billaud and Magadur, 1992) The rarity of PMR at this time may be explained by a lack of awareness of the condition, rising life expectancy or a genuine increase in the incidence of PMR since that time. A trend of increasing incidence and prevalence was seen in the work of Smeeth, Cook, and Hall (2006). The third paper from Eaton et al, which reported a prevalence of 0.3%, looked at a wide range of auto-immune diseases and was published much more recently. However, it used all adult patients as the denominator rather focussing on older adults, and hospital rather than primary care records, leading to a lower prevalence estimate than other contemporaneous studies. (Eaton et al. 2010)

Overall, contemporary estimates of PMR prevalence suggest it is likely to affect between 0.5-1% of the population in countries with high numbers of people with northern European, and potentially also Mediterranean genetic heritage. The studies which show the highest prevalence are community based and there appears to be a trend of increasing PMR prevalence over time.

1.13 Limitations of existing studies

There are a number of limitations to the studies that have reported data on the incidence or prevalence of PMR. The majority of studies were performed in secondary care settings likely leading to an underestimate of disease burden of PMR. Whilst some primary care estimates exist, the number of studies available are limited. It has been estimated that in the UK the number of people aged 65 and over will increase by around two thirds between 2008 and 2032. (Dunnell, 2008) As the population of the United Kingdom continues to rapidly age, the lack of contemporaneous data of the epidemiology of PMR is concerning.

1.14 Conclusion

PMR has been recognised as a medical condition since the 19th Century and, in the UK, is mainly treated in primary care. However, a number of important clinical quandaries around PMR remain. First, estimates of the incidence and prevalence of PMR vary by almost a factor of ten depending on study design and location. Second, concerns remain regarding the existence of a cohort of patients who are

subject to prolonged glucocorticoid therapy given the long term effects of this therapy and potential impacts on inter-current comorbidity. Finally, current guidelines suggest that PMR is a diagnosis of exclusion, with an extensive list of conditions which preclude diagnosis, despite the fact that some of these comorbidities are common in the age group typically affected by PMR.

In order to address these concerns, this thesis contains an up-to-date, large scale epidemiological study of the incidence, prevalence and treatment of PMR in UK primary care. Following this, a systematic review of literature will assess the current evidence around multimorbidity and the general health status of patients with PMR. Finally, large scale epidemiological case control and cohort studies will attempt to address gaps in the literature of the comorbidities associated with PMR, and the general health of patients with PMR both before and after diagnosis.

This will create an up to date, detailed picture of the burden that PMR imposes on the UK healthcare system and the overall health of patients with a diagnosis of PMR. In achieving this it may then be possible to recognise that PMR can co-exist with other common comorbidities as well as identifying whether any specific comorbidities are more common in patients with PMR.

The following chapter explains the way in which these questions will be addressed.

Chapter 2 CLINICAL PRACTICE RESEARCH DATALINK

This chapter will describe the Clinical Practice Research Datalink (CPRD), the data source used for this thesis. This will include how the data is collected, its demographic composition in relation to the UK population, the strengths and weaknesses of the dataset and which alternative datasets are available.

2.1 Ethical considerations and research approval

Formal ethical approval was not required as the Clinical Practice Research Datalink (CPRD) has generic ethical approval. However, in order to conduct publishable research, permission must be granted by the Independent Scientific Advisory Committee (ISAC). This committee was established by the Secretary of State for Health in February 2006 to review proposals for research using the MHRA's CPRD and Yellow Card Scheme databases.

The ISAC committee assesses the feasibility, quality and public health value of research studies proposing to use anonymised patient level data from the CPRD. It provides high-quality peer reviews on the scientific merit of research proposals submitted to them, and examines the medical, epidemiological and methodological merits of proposed studies. (ISAC, 2017) The ISAC committee include scientific and lay members. Scientific members provide advice on the medical, statistical, epidemiological and methodological aspects of protocols. Lay members provide advice where there may be potential governance issues associated with a study. Approval for this study was granted following the completion and successful review of the ISAC protocol form, (protocol number:

17_203RA), a copy of which is included as Appendix 1. This approval process also provides further assurance that the methodologies employed in the studies described are robust.

The CPRD is based on data taken from UK primary care. The following section describes the place of primary care within the UK healthcare system.

2.2 UK Primary Healthcare System

Almost all healthcare in the United Kingdom (UK) is delivered by the National Health Service (NHS). The NHS was founded following the Second World War in 1948, with the aims of providing universal, equitable and centrally funded healthcare that was free at the point of delivery. (Delamothe, 2008) It remains a public system funded by taxation and continues to provide free, or low-cost, healthcare to all residents of the UK.

Around 90% of patient contact in the UK with the NHS is via primary care. (Hippisley-Cox and Vinogradova 2009) Primary care within the NHS is largely delivered by general practices. These are generally small, physician led organisations run on behalf of the NHS that are responsible for patients who live within a defined and agreed geographic area. (Roland, Guthrie, and Thome 2012) Each person within the United Kingdom is entitled to register with a General Practice, and around 98% of the UK population are indeed registered with a practice. (Office for National Statistics 2012)

Practices may employ a wide variety of healthcare professionals, including General Practitioners (GPs), Nurses, Pharmacists, Nurse Practitioners,

Occupational therapists, Psychologists, Counsellors and Paramedics. (Freund et al., 2015) The average population size each practice serves has increased over the last decade, as has the workload that each practice has to shoulder, (Grosios, Gahan and Burbidge, 2010) evidenced by the increase in the average number of consultations per patient per year. (Baird et al., 2016)

Almost all general practices in the United Kingdom now use electronic healthcare records (EHR) to record patients' medical information, although the choice of software used is dependent on the practice. (Roland, Guthrie and Thome, 2012) This includes software such as VISION® (Vision Electronic Health Record System, 2018) EMIS® (EMIS Electronic Health Record System, 2018) and SystmOneGP®. (SystmOne Electronic Health Record System, 2018) The shift to EHRs was, in part, following the introduction of the 'Quality and Outcomes Framework' (QoF). This scheme incentivised GPs by offering an increase in practice income of around 25% provided they achieved certain 'targets' in quality of care. In order for the attainment of these targets to be recorded and rewarded, EHRs were necessary, leading to the adoption of paperless records. (Roland, Guthrie and Thome, 2012) The system used to record and store diagnoses and other clinically relevant information in UK primary care is the Read code system, which is a hierarchical coded thesaurus of clinical terms. (NHS Digital, 2017)

As well as primary care data, clinical diagnoses and treatments made in secondary and tertiary care are also recorded and coded in the EHR in UK primary care. This is because general practices act as the hub of the UK healthcare system. The GP is the gatekeeper of care for all non-emergency health problems in the UK and is responsible for referring patients for specialist

input. Therefore, each time a patient is seen in another NHS care setting, whether this is as an inpatient or outpatient, a summary of the outcome of this event is sent to the patient's General Practice. The data in the summary is then coded and added to the patient's EHR.

GPs in the UK are expected to practise to a high clinical standard. The performance of GPs and practices are independently monitored through appraisals, QoF monitoring and Care Quality Commission (CQC) inspections. Clinical guidelines are published by the National Institute for Health and Care Excellence, which GPs are expected to follow to ensure best practice is followed. Therefore, management of disease should not vary greatly by practice or GP. As such, information taken from primary care data will reliably reflect disease epidemiology and management in the UK.

In conclusion, the NHS achieves almost universal population coverage. Within this system General Practices, who act as information gatherers in the healthcare system, have enthusiastically adopted robust EHRs. The result of this is primary care services in the UK have longitudinal, electronically coded, contemporaneous and comprehensive clinical information recorded during routine clinical care for a large proportion of the UK population. These clinical records therefore provide an invaluable resource for collecting epidemiological data particularly around conditions, such as PMR, which are predominantly treated in primary care.

2.3 Data Source

The data source that was used in this study is the Clinical Practice Research Datalink (CPRD). The CPRD is a governmental, not-for-profit research service that has been established for more than thirty years. It is a joint venture between the Medicines & Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR), which is owned by the Department of Health (DoH) and operates within the NIHR. (ISAC, 2017)

The CPRD began as a small local database named Value Added Information Medical Products (VAMP) before expanding and being renamed General Practice Research Database (GPRD). Subsequently, control was passed to the MHRA and the database evolved into the CPRD.

The CPRD exists due to the underpinnings provided by primary care EHR. The decision to contribute data to CPRD is voluntary and taken by individual practices, who do not receive financial reimbursement. Once a practice has enrolled all patients within the practice are automatically added, however they have the right to opt out of collection of their data at any time. CPRD contains anonymised information from 718 UK General Practices (7.5% of the total) and has over 17 million medical records from patients registered with one of these practices. The anonymisation procedure involves two separate processes in order that patient identifiable data is not visible either to external researchers or data processors within the CPRD.

Two different levels of access to the CPRD exist, ‘GOLD’ and ‘AURUM’. CPRD GOLD contains information contributed by practices using VISION® software,

while AURUM contains data from practices utilising EMIS Web®. Each research institute that wishes to use CPRD must pay a fee to access it, in order that the DoH can continue to invest in, and develop, the dataset.

The CPRD contains information across several domains, including patient demographics, diagnoses, symptoms, signs, prescriptions, referrals, immunisations, behavioural factors and tests. (Herrett, Gallagher, et al., 2015) Each new entry into a patient's records creates a new line of data, to which information such as the date when the entry was added, the date to which it pertains, and the staff member inputting data, is recorded. There can be differences between dates of entry and the date upon which the event the entry is referring to occurred, for example if an entry was made retrospectively following an event. Information around which staff member inputs data is limited to a numerical identifier for each member of staff, therefore this too is anonymised.

In order for data to be captured within the CPRD, the healthcare practitioner must select and enter a Read code. CPRD does not record when free text is inputted into records as a further precaution to ensure anonymity. Each Read code, which is a combination of numbers, letters and full stops, is translated to a unique Medical code in CPRD. This Medical code can then be used to identify which patients have a certain diagnosis. As the Medical code is composed only of numbers rather than combinations of symbols, data is simpler to process. Geographic information is divided into 10 regions of the UK. GPs are encouraged to record all encounters with patients and code any clinical information, therefore not all entries will reflect a 'face to face' appointment. The stored patient data is

anonymised and complies with existing ethical, governance and security regulations and frameworks.

Each patient who contributes data to CPRD has a number of individual dates attached to their record indicating when they joined or left the database. These dates include: 1) the first registration date (frd), which is the date when a patient first joined the contributing practice; 2) the current registration date (crd), the date when a patient most recently joined the contributing practice; and 3) the up-to-standard (uts) date, which is the date at which the practice was adjudged to reach internal quality standards.

Indications that a patient has left the database include: 1) the transfer out date (tod), which is the date the patient left a practice; 2) the last collection date (lcd), the last date that data was collected from this practice; and 3) the date of death for a patient, if recorded.

To increase the scope of the database beyond purely primary care, a subset of practices in England has been linked to other registries, for example Hospital Episode Statistics (HES). This provides access to data for these patients taken directly from secondary care. Other registries that patients in CPRD can be linked to include ONS mortality data and patient level index of multiple deprivation data. These provide more detailed information on deaths and the level of social deprivation in the area that the patient lives. This feature is valuable given that it has long been established that high levels of deprivation are strongly linked to social deprivation. (Rose and Marmot, 1981)

CPRD can therefore supply extensive primary care based and linked secondary care patient data to researchers in the UK as well as internationally. Furthermore,

its use in rheumatology research has already been established by previous studies investigating PMR (Hancock et al., 2014; Muller et al., 2014) and other inflammatory rheumatological conditions, such as rheumatoid arthritis, gout and systemic lupus erythematosus. (Garcia-Rodriguez et al., 2009; Edwards et al., 2012; Rees et al., 2014)

2.4 CPRD strengths and weaknesses

Strengths

The CPRD database has been established for over 30 years and has been shown to be representative of the UK population in terms of age, sex and ethnicity; (Herrett, Gallagher, et al., 2015) furthermore it has been used extensively for primary care research. The CPRD employs rigorous internal checks and mechanisms to ensure that practices reach internal quality standards with the data they contribute. The date at which a practice attains this level is given in the data as the 'up-to-standard' date. Therefore, data collection can be limited to only that recorded after this event.

The CPRD covers an extraordinarily large number of patients within a national health organisation. Such a large dataset has particular advantages, for example when looking to study relatively rare diseases where a large population is required to obtain sufficient sample size. (Dommett et al., 2012; Douglas et al., 2013) The information recorded in CPRD is entirely clinical in nature, and is not driven by insurance or billing needs. Therefore, the database is less likely to exclude those who are from socioeconomically deprived or isolated backgrounds

who may not have health insurance or be able to access private healthcare. Furthermore, systems which are based upon billing information may inadvertently incentivise over-investigation or over-diagnosis by physicians whereas CPRD avoids this pitfall.

The CPRD draws its data from routinely collected primary care. A subject of debate in clinical research surrounds the use of stringent inclusion and exclusion criteria in the selection of research subjects. Some researchers have questioned whether this may inadvertently lead to unbalanced recruitment of patients and reduced generalisability. (Kennedy-Martin et al., 2015) CPRD includes data on all patients with diagnoses made in the course of routine clinical care, with no inclusion or exclusion criteria. Therefore, research performed using this database has high generalisability to other patients in the UK and potentially further afield.

Furthermore, the CPRD operates within stringent UK and European Union (EU) data protection laws, including the General Data Protection Register (GDPR), which work to ensure protection of patient information. A further layer of security to preserve patient anonymity is added by CPRD as it holds patient identifying and clinical data separately.

Weaknesses

Due to the way data is collected, clinical information is added only when patient records are updated. Therefore, the frequency of data collection is determined by patient attendance or contact with their GP. This is different to formal medical research studies in which data will be collected at pre-defined time points

following, for example, administration of therapy. As CPRD is a database of routine medical care irregular, or loss to, follow up is inevitable. However, it could be argued that this loss more accurately reflects typical patterns of illness in real life situations, providing information that is more reflective of actual clinical practice.

Diagnoses in CPRD, as discussed, are based on the presence of a Read code for a disease. This means that a patient has been adjudged by a healthcare practitioner to satisfy diagnostic criteria for a condition. This threshold over which a disease is diagnosed is therefore likely to be different than would be seen in a controlled research study. Alongside this, the stringent inclusion and exclusion criteria which exist in many clinical studies do not exist in routine primary care. This would have the effect that, compared to patient samples used in research studies, patients diagnosed in primary care will form a much less homogenous group. This, however, improves the generalisability of the sample of patients selected as they are more likely to be representative of people with this condition in the general population.

The use of Read codes to make a positive diagnosis necessitates that the opposite situation also applies, i.e. that the absence of a Read code must be interpreted as an absence of that disease. This may mean that some patients who have the symptoms of a disease but haven't had a disease code recorded will not be captured by this dataset. Therefore, although positive predictive value tends to be high in CPRD, sensitivity may be lower. (Herrett, Thomas, et al., 2010) Furthermore, once a Read code is recorded, they are not often removed from a patient's EHR. This could mean, for example in the case of PMR, even if

a patient was subsequently diagnosed with rheumatoid arthritis (RA) both codes would remain in their EHR.

CPRD provides access via linked datasets to information about deprivation indices, however there is limited access to socioeconomic data such as employment status which could provide further context to a patient's health status. Also, as CPRD has been evolving for thirty years the extended features, such as data linkage, which are available in current and recent data, may not be available or incomplete depending on how far back in the dataset data is required, for example there is no access to test results prior to 2002.

A final drawback to CPRD is the cost to gain the CPRD gold licence in order to obtain access to the dataset. This is considerable, at approximately £125,000 per year and is therefore beyond the means of individuals and many departments without significant resources. The cost in this study has been met by Keele University Research Institute for Primary Care and Health Sciences through pooled funding applications to undertake a range of CPRD related studies.

2.5 Alternative data sources

CPRD is one of three major primary care databases in the United Kingdom. The other two are QResearch and The Health Improvement Network (THIN).

QResearch is a large primary care database which contains information on over 12 million patients. (Chaudhry et al., 2017) The database is a non-profit collaboration between the University of Nottingham and Egton Medical Information Systems (EMIS). EMIS, as discussed earlier, is one of the three main

software platforms on which EHRs are based in UK primary care. QResearch, like CPRD, is anonymised and has continuing research and ethical approval from the East-Midlands – Derby Research Ethics Committee.

THIN is a collaboration between In Practice Systems Ltd (INPS) and IQVIA, a company formed from a merger of IMS Health and Quintiles. INPS are responsible for the VISION EHR system. THIN data collection began in 2003 and the total number of patient records within the database is over 11 million. (Chaudhry et al., 2017)

Of the three databases, CPRD has both the longest follow up and largest sample size. It also offers, for a cost, access to data taken both from VISION and EMIS systems, which is in contrast to QResearch and THIN. The way that data is recorded differs slightly between the EHRs. For example, the VISION EHR system is structured to record data using problem oriented medical records (POMR), rather than episode oriented medical records (EOMR). In POMR, medical and drug information must be linked to a specific coded problem, in contrast EOMR requires linkage to episode data. It has been postulated that by ensuring practitioners link clinical or prescribing data to a specific code reduces intra-patient coding variability, increasing data quality. (De Lusignan et al., 2015)

As well as CPRD being larger in size and established longer, a greater number of academic articles have been published using CPRD data. A recent study found, between the years of 2004-2013, a total of 1,296 studies were published using data from one of these datasets. Of these, 825 (63.6%) used CPRD data, while 394 (30.4%) and 77 (5.9%) used THIN and QResearch respectively. As such, CPRD is more widely recognised and utilised in medical research.

CPRD is the longest established, largest and most referenced primary care database in the United Kingdom, therefore this was the resource selected for use in this thesis.

2.6 Composition of CPRD

CPRD has been established for over 30 years. The studies described in this thesis will begin in 1990 which will allow an investigation into whether any trends in the incidence and prevalence of PMR are present over a prolonged time period. During this period, the number of practices, and therefore patients, contributing to CPRD has changed, (figure 2-1) as has the size of contributing practices (figure 2-2).

Figure 2-1: The number of patients and practices contributing data to CPRD each calendar year (1990-2016)

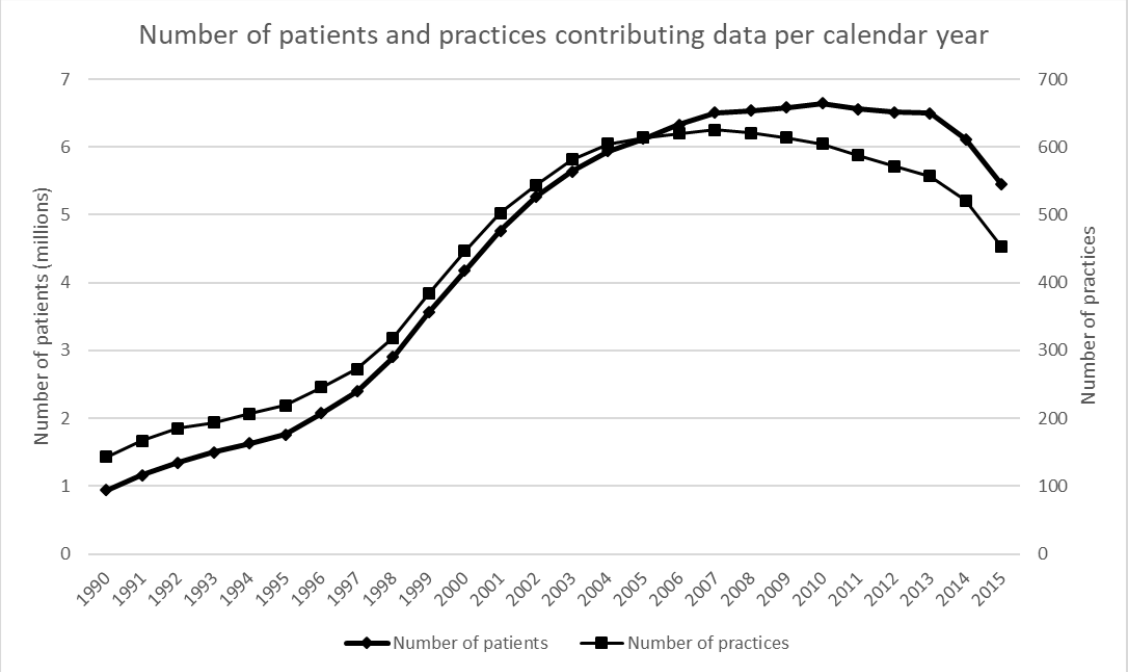
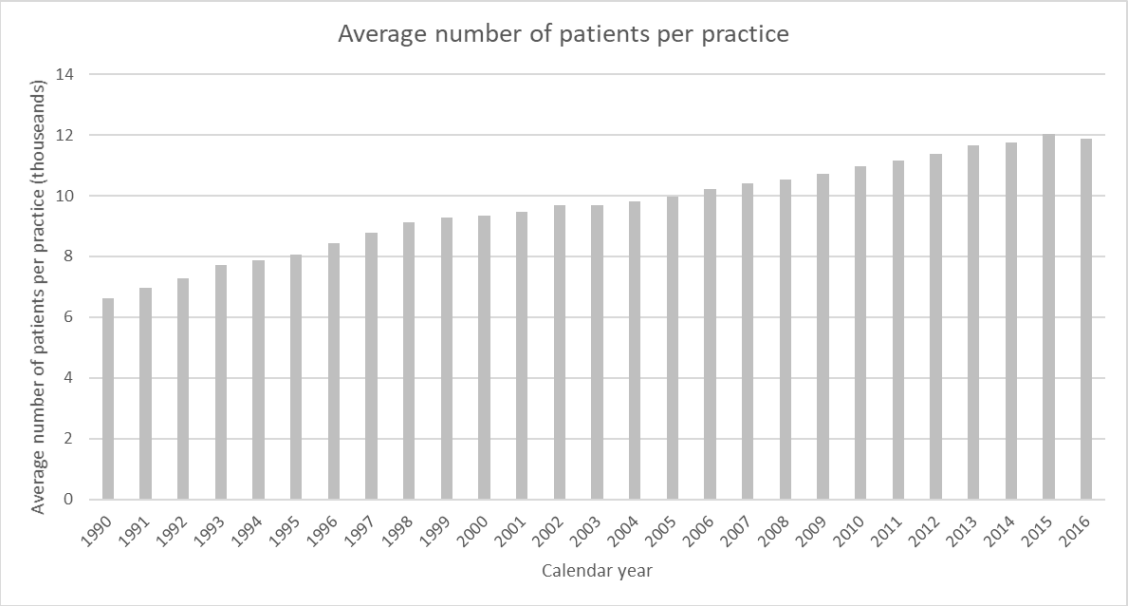


Figure 2-2: The mean number of patients registered with a contributing CPRD practice (1990-2016)



The total number of patients contributing data to CPRD in any one calendar year has increased from around 1 million patients in 1990, to a peak of almost 7 million patients in 2011-2013. The number of contributing practices has declined since 2013, which may be due to practices changing to an alternative EHR. This may have been an indirect consequence of the Health and Social Care Act (2012). This act mandated the formation of CCGs (Clinical Commissioning Groups), by GPs in order to commission services in their local area. This change meant that greater harmonisation between practices was necessary and led to practices in each area selecting a single EHR.

In common with all practices in the UK, the average numbers of patients registered with each practice contributing to CPRD has increased. This has been driven by a number of factors, including the rapid decline in the number of "single-handed" GP practices and corresponding increase in the number of practices formally amalgamating together. (Goodwin et al., 2011)

2.7 Descriptive statistics: a comparison between CPRD and UK population structures

Descriptive statistics were used to describe demographic data of the CPRD and UK populations. In order to assert that CPRD continues to be representative of the UK population, the demographics of people alive and contributing data to CPRD in the latest full year of available data was compared to the general population. Demographic data available in CPRD includes age, sex and the region in which a practice is based. In CPRD, to help preserve anonymity, a patient's exact date of birth is not given, instead the year of birth is recorded and from this the approximate age can be calculated. Sex and region data are coded as in table 2-1.

Table 2-1: Coding of demographic characteristics in CPRD

Demographic characteristic	**Code**
Sex	
Male	1
Female	2
Region	
North East	1
North West	2
Yorkshire & the Humber	3
East Midlands	4
West Midlands	5
East of England	6
South West	7
South Central	8
London	9
South East Coast	10
Northern Ireland	11
Scotland	12
Wales	13

To compare demographic data in CPRD and the UK population, information was extracted from CPRD and the mid-year estimates of the UK population in 2016 published by the Office for National Statistics (table 2-2). (Office for National Statistics, 2016) In this table, the UK data is compared to CPRD both in total numbers and proportion, and then further stratifies the data by sex, age and country of origin.

Table 2-2: Demographic characteristics of UK population compared to patients actively contributing data to CPRD in 2016

Number of patients	**UK population (%)**	**CPRD 2016 (%)**
Total	65,648,100 (100)	4,285,741 (100)
Sex		
Male	32,377,700 (49.32)	2,067,411 (48.24)
Female	33,270,400 (50.68)	2,218,330 (51.76)
Age in 2016		
0-9	8,051,800 (12.27)	418,219 (9.76)
10-19	7,404,000 (11.28)	441,854 (10.31)
20-29	8,764,400 (13.35)	517,109 (12.07)
30-39	8,587,700 (13.08)	574,786 (13.41)
40-49	8,793,200 (13.39)	601,635 (14.04)
50-59	8,698,700 (13.25)	573,261 (13.38)
60-69	7,170,700 (10.92)	460,821 (10.75)
70-79	5,006,600 (7.63)	357,647 (8.34)
80-89	2,599,700 (3.96)	223,802 (5.22)
90+	571,200 (0.87)	116,607 (2.72)
Country		
United Kingdom	65,648,100 (100)	4,286,456 (100)
England	55,268,100 (84.19)	2,667,873 (62.25)
Northern Ireland	1,862,100 (2.84)	210,067 (4.90)
Scotland	5,404,700 (8.23)	676,994 (15.80)
Wales	3,113,200 (4.74)	730,807 (17.05)

The proportion of males and females in the UK population and CPRD data are similar, with a slightly smaller proportion of men in CPRD compared to the UK population. This is likely due to reduced utilisation of healthcare services in men

compared to women. (Wang et al., 2013) Relating to the regional distribution of practices, CPRD is relatively under-represented in patients from English practices compared to Northern Ireland, Scotland and Wales. This is likely due to variations in uptake of different EHR software by region. However, the genetic variation within UK is relatively low, (Leslie et al., 2015) and therefore the generalisability of CPRD data is maintained. To allow easier visualisation of the population structure of CPRD and the United Kingdom, population pyramids were created using this data (figures 2-3 and 2-4).

Figure 2-3: Population pyramid of patients contributing data to CPRD in 2016

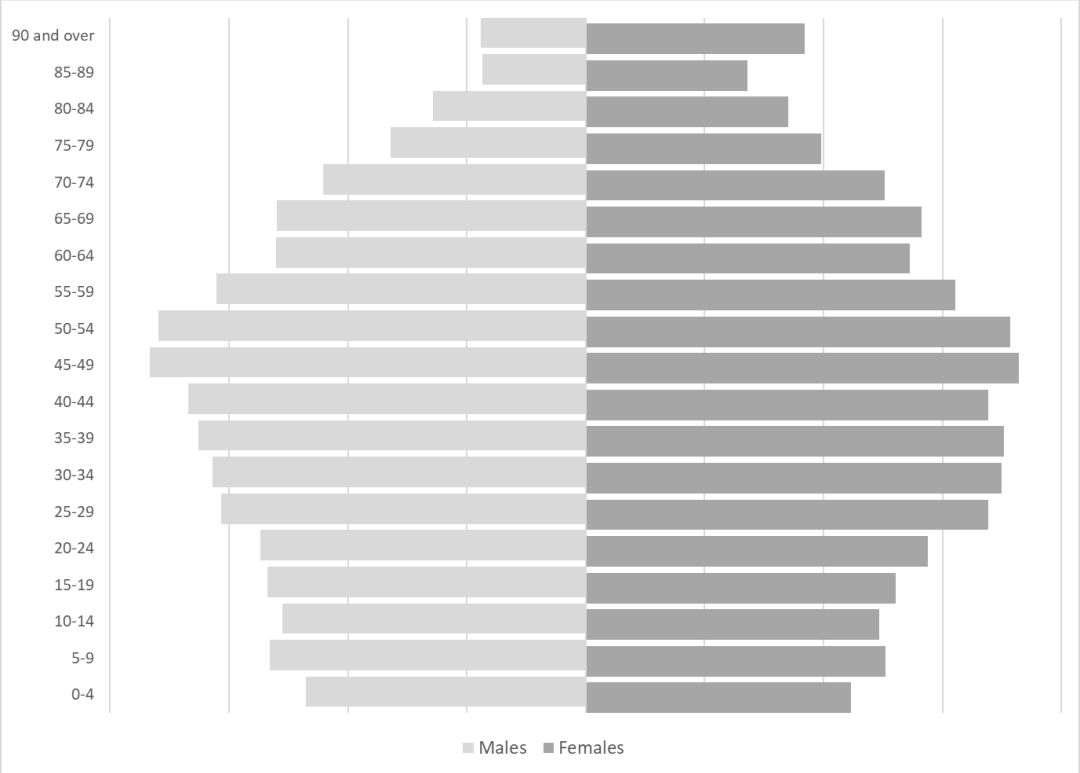
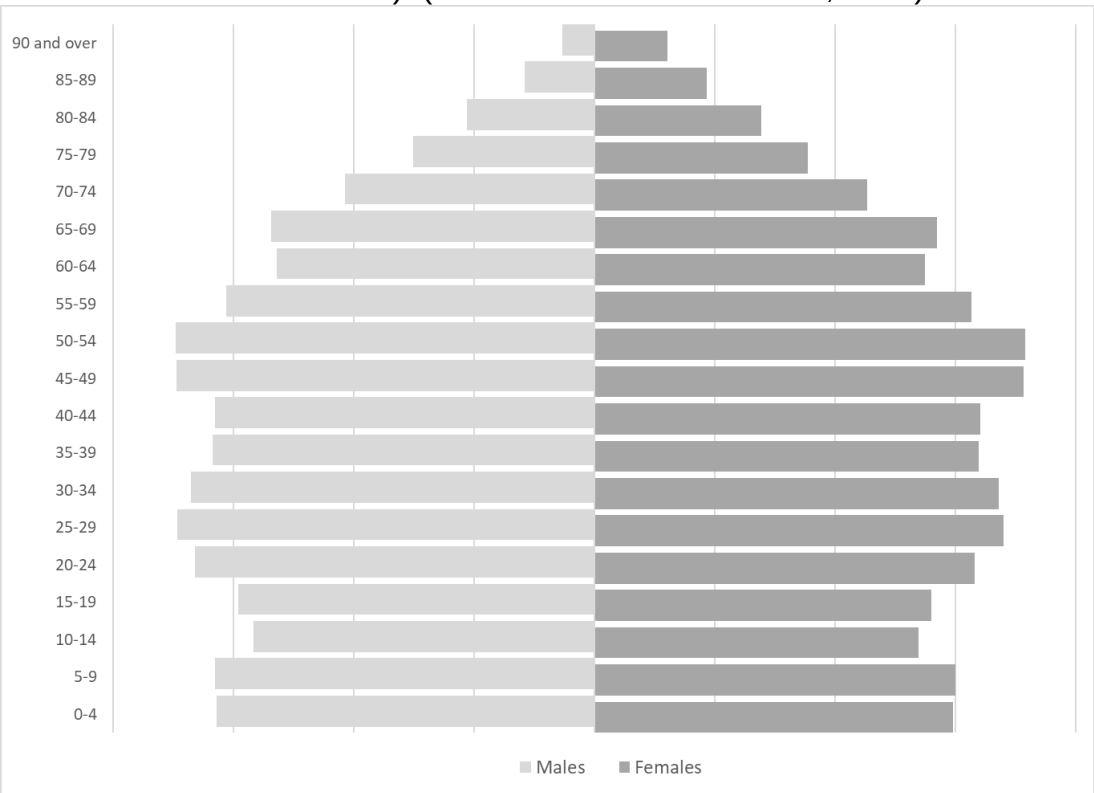


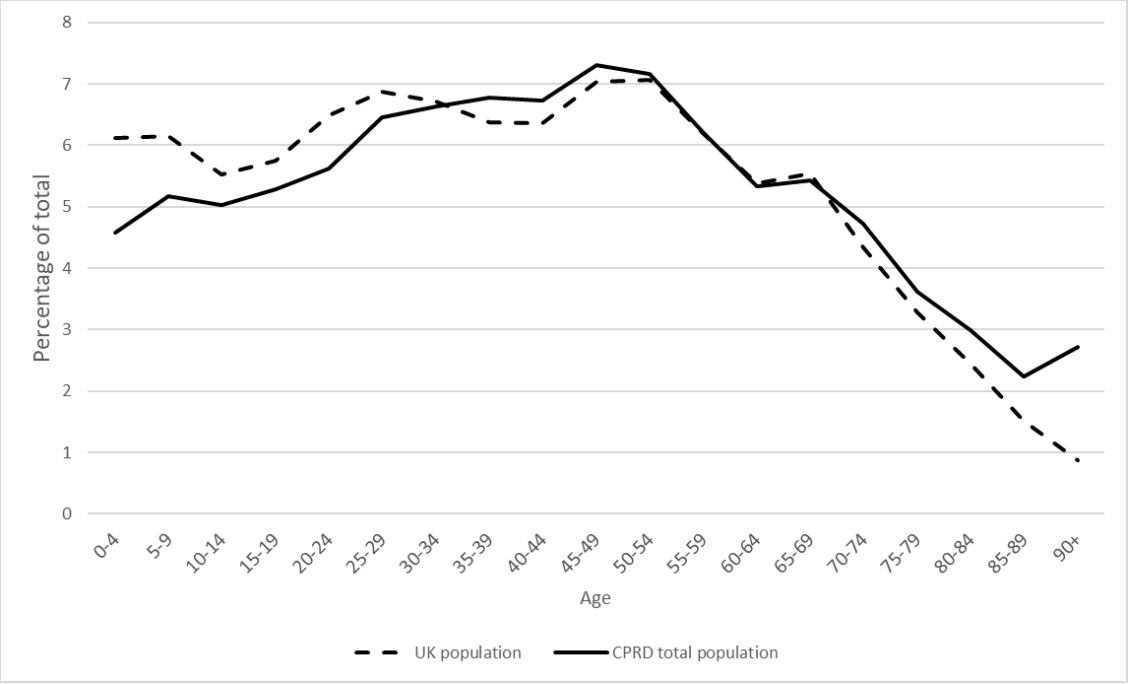
Figure 2-4: UK population pyramid derived from mid-year estimates (2016) from Office for National Statistics). (Office for National Statistics, 2016)



Both of these distributions correspond to a stage 4, contractive, population pyramid. Societies in this stage of population development have a declining birth rate, long life expectancy and a low death rate. The UK population is gradually ageing. In 1974 the ages at the 25th centile, median and 75th centile were 15.9, 33.9 and 54.8; by 2014 this had increased to 21.1, 40 and 58.3 respectively.

Although the two distributions are broadly similar, there appears to be some differences particularly at the extremes of age, where a greater proportion of older people and a smaller proportion of young people are contributing to CPRD compared to what you would expect given the overall UK population distribution. Below is a direct comparison of the population distribution (figure 2-5).

Figure 2-5: Age distribution of patients enrolled in CPRD compared to UK population 2016. (Office for National Statistics, 2016)



It can be seen that the population distribution of patients contributing to CPRD closely approximates the UK population distribution between the ages of 25-29 until 45-49; after which the distributions appear to be almost identical. However in under 25s and over 75s there is some divergence.

The likely reason for this is that children and young people are less likely to present for review to their General Practitioners; as such they are also less likely to contribute data to the CPRD. Furthermore, this explains the reason why older patients are overestimated in CPRD, as they are more likely to be subject to active surveillance or follow up with multiple conditions, given that multi-morbidity and therefore need for access to medical services, is strongly associated with increasing age. (Salive, 2013)

Figures 2-6 and 2-7 illustrate population data stratified into male and female distributions respectively. The difference at younger ages is accentuated in males, and there is also an increase in the proportion of male patients in the CPRD dataset who are entering early middle age (40-50 years old) compared to the overall population. These differences are likely explained by reduced male utilisation of primary care services in early adulthood (Wang et al., 2013) but then earlier development of chronic illness in men compared to women. (Oksuzyan et al., 2008)

The difference between CPRD and the UK population structure in women is much less at a younger age and closely approximates the UK population for most of the age bands. The most pronounced difference between the UK and CPRD populations is found at the extreme of age; this again is likely a reflection of the

greater lifespan of women and the inevitable increase in the use of health services by patients who are older.

Figure 2-6: Age distribution of male patients enrolled in CPRD compared to UK population 2016. (Office for National Statistics, 2016)

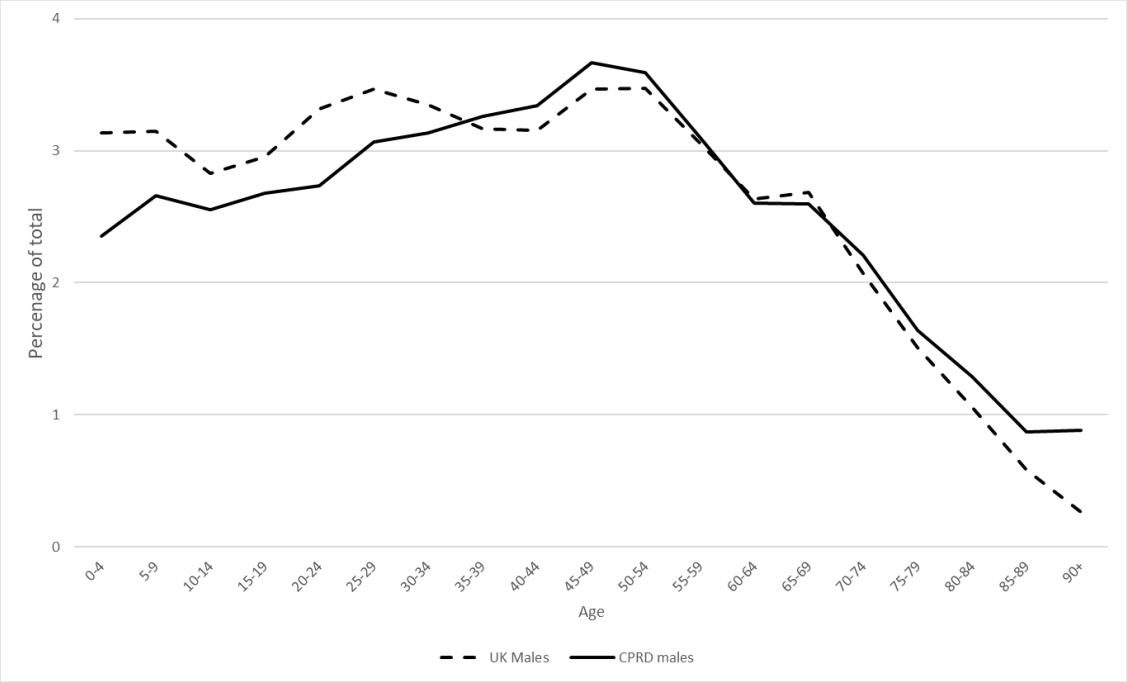
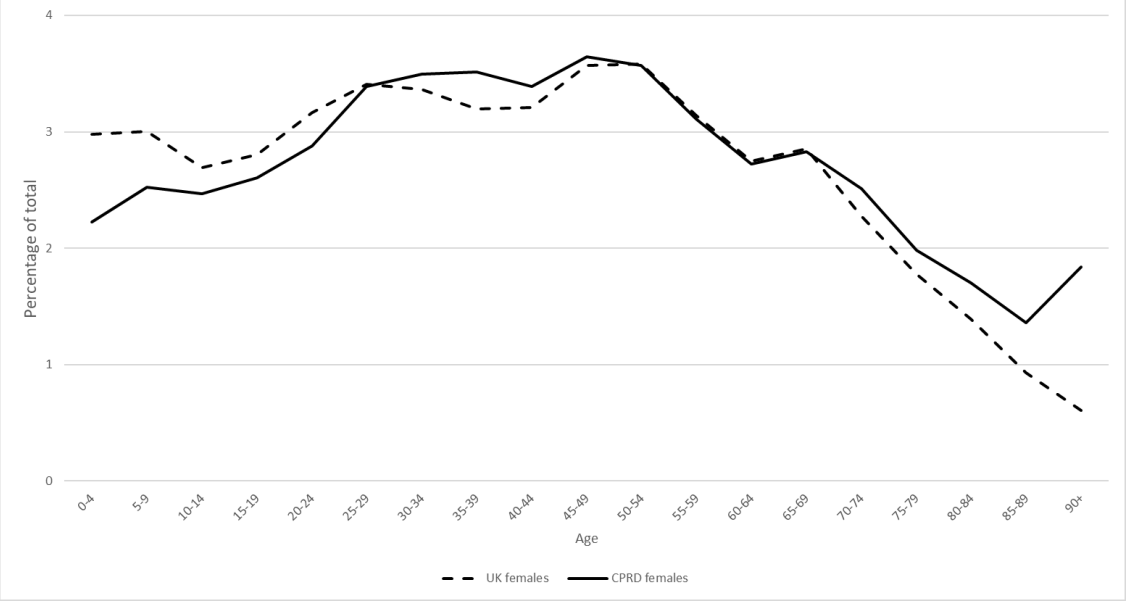
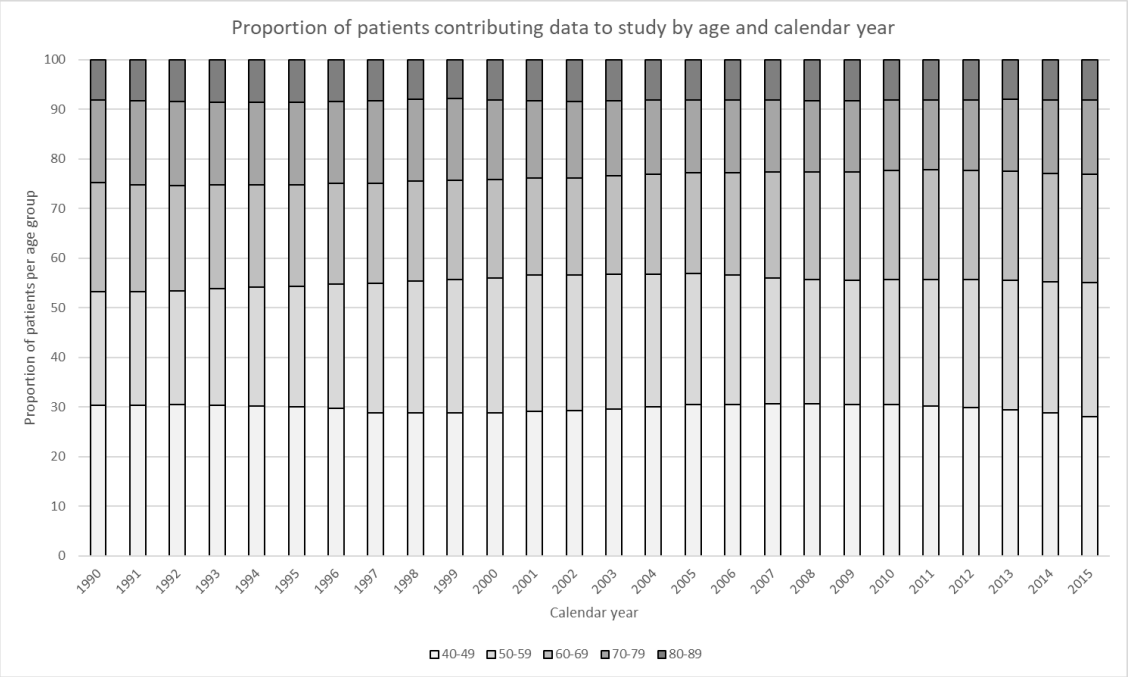


Figure 2-7: Age distribution of female patients enrolled in CPRD compared to UK population 2016. (Office for National Statistics, 2016)



Having established the age distribution of people actively contributing data to CPRD in 2016 is similar to the UK population at the same time, it is important to assess whether this distribution is steady throughout the whole study period. Figure 2-8 illustrates the age distribution of patients in CPRD from 1990-2015 and shows that the proportion of people within each age band remains similar across the whole study period.

Figure 2-8: Proportion of people contributing data to CPRD, 1990-2015, stratified by age



Therefore, it can be asserted that the CPRD database contains data on patients who are similar to the wider UK population, based on age, sex and geographical location. The differences observed in the population with regards to age group and sex are related to variations in utilisation of healthcare in these groups. Due to the way CPRD data are collected, whereupon patients only contribute data when they are followed up, these differences are inevitable. Regarding the

geographic variation, as discussed previously, practices are recruited to CPRD voluntarily. This will likely lead to clustering of practice recruitment in which a single practice initially joins and then provides positive feedback of the process to neighbouring organisations or alternatively where groups of practices join together following discussions at higher management, such as CCG, levels. As genetic variation between the constituent countries of the UK is low this is unlikely to affect the generalisability of results.

2.8 Comparison between CPRD and HES linked patients

Having established that the CPRD as a whole is representative of the UK population, further comparison is required to ascertain whether patients who contribute to CPRD and are from practices linked to secondary care datasets (section 2.3) are similar to the CPRD database as a whole. The demographic characteristics, stratified by sex, age and country, of patients contributing to CPRD in 2016 and those with linkage are summarised in table 2-3.

Table 2-3: Comparison between CPRD and linked patients

	CPRD 2016 (%)	CPRD & linkage (2016)
Number of patients		
Total	4,285,741 (100)	1,697,629 (100)
Sex		
Male	2,067,411 (48.24)	827,693 (48.76)
Female	2,218,330 (51.76)	869,936 (51.24)
Age in 2016		
0-9	418,219 (9.76)	194,092 (11.43)
10-19	441,854 (10.31)	183,236 (10.79)
20-29	517,109 (12.07)	203,862 (12.01)
30-39	574,786 (13.41)	230,742 (13.59)
40-49	601,635 (14.04)	237,692 (14)
50-59	573,261 (13.38)	230,599 (13.58)
60-69	460,821 (10.75)	179,995 (10.6)
70-79	357,647 (8.34)	133,836 (7.88)
80-89	223,802 (5.22)	78,195 (4.61)
90+	116,607 (2.72)	25,380 (1.49)
Country		
United Kingdom	4,286,456 (100)	1,697,629 (100)
England	2,667,873 (62.25)	1,697,629 (100)
Northern Ireland	210,067 (4.90)	
Scotland	676,994 (15.80)	
Wales	730,807 (17.05)	

From this data, it can be seen that the age ranges of the patients with linkage established are similar to those who only contribute to CPRD; as are the proportions of male and female patients. However, the country of origin is clearly different. This is due to the fact that healthcare is a devolved area. Healthcare is therefore the responsibility to the governments of Northern Ireland, Scotland and Wales and, as a result, are run along slightly different models to England. Therefore, access to linked data is only available between general practices and hospitals in England. However, overall, the demographics of the linked data is similar to the CPRD dataset. The next section will describe how PMR cases were identified in CPRD.

2.9 Case definition of polymyalgia rheumatica

As previously discussed, case ascertainment in CPRD is defined by the presence of a Read code to indicate a positive diagnosis, the list of differential diagnoses in PMR is wide, (Kermani and Warrington, 2013) and no specific autoantibody exists to allow confirmation of diagnosis. (Floris et al., 2018)

Therefore, the presence of a Read code alone may not be considered sufficient to establish whether a diagnosis of PMR has definitively been made. In order to improve case ascertainment, a PMR diagnosis was only considered to be valid if patients received at least two prescriptions for oral glucocorticoids; one within six months of the diagnosis date and the second within six months of the first prescription. This mirrored the approach taken in a number of other CPRD studies of PMR, including the most comprehensive estimate of its incidence by Smeeth et al (Smeeth, Cook and Hall, 2006) as well as other more recent publications. (Muller et al., 2014; Pujades-Rodriguez et al., 2016)

Given the strong association between PMR and GCA, patients who also had this diagnosis were included. The Read codes used to identify patients with PMR were: N20..00 Polymyalgia rheumatica and N200.00, Giant cell arteritis with polymyalgia rheumatica. To further enhance case ascertainment, all patients who were below the age of 40 were excluded. PMR is rare in this age group and is likely to represent significantly atypical disease or an incorrect diagnosis.

2.10 Case definition of glucocorticoid prescriptions

In order to identify glucocorticoid (GC) prescriptions in patients with PMR, all GC prescriptions recorded in CPRD using medications from the British National Formulary (BNF) chapter 6.3.2 “Glucocorticoid therapy” were included. (Royal Pharmaceutical Society, 2017) These included prednisolone, deflacort, dexamethasone, hydrocortisone, methylprednisolone and triamcinolone. All GC prescriptions that were orally or parenterally administered were included, and topical preparations were excluded. CPRD contains the name of the medication, the quantity prescribed, number of units of medication to be taken each day and prescription duration. The BNF produces a glucocorticoid equivalence chart in which the different potencies of different glucocorticoids are published. (Royal Pharmaceutical Society, 2017) Using this, all prescriptions were converted into strength equivalent to 5mg prednisolone.

2.11 Case definition of comorbidities

The comorbidities that were assessed during this study were identified using three sources: the Charlson comorbidity index, (Charlson et al., 1994) the results of a systematic review (chapter 5), and consultation with experts in the management of PMR, including both rheumatologists and GPs. This process is explained in detail in chapter 6.2.7. In this section, the Charlson comorbidity index and the process through which code lists for each comorbidity were produced are described.

The Charlson comorbidity index is a list of common chronic medical conditions in which each is assigned a score, the total of which is a useful predictor of mortality risk. (Charlson et al., 1994) The index contains 17 diagnostic categories across a range of health domains, and the value assigned to each is based on the severity of each condition. These conditions include vascular diseases such as myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease; as well as other conditions such as chronic pulmonary disease, dementia, diabetes mellitus (DM), or DM with chronic complications, rheumatological disease, peptic ulcer disease, renal disease, any malignancy (including leukaemia and lymphoma), metastatic solid tumour, mild liver disease, moderate or severe liver disease and HIV infection. The score that a patient obtains is therefore suitable to give an overview of an individual's health status. This list has been used previously in studies of comorbidity in other inflammatory rheumatological diseases. (Kuo et al., 2016)

The process through which comorbidities of interest for this study were identified is described in chapter 6.2.7. Once these comorbidities were identified, lists of Read codes were produced for each comorbidity. In contrast to PMR, which only has two diagnostic Read codes, many of the comorbidities investigated had multiple different Read codes to signify diagnosis. These can reflect severity of disease, for example chronic kidney disease stages, or different presentations of a similar pathological process, for example myocardial infarction or angina. In order to capture each relevant diagnosis, robust lists of Read codes were constructed.

The lists were constructed using the CPRD Medical Browser v1.4.0. This browser is searchable by Read code, Medical code and Read Terms. Medical codes, as previously discussed, are unique numerical codes for each Read code. Read Terms are a description of what each Read code signifies. When searching in this browser there is the facility to use an asterisk, which enables a search for any Read Term which begin with the letters selected. As well as providing information on the Medical codes necessary, the browser also gives information as to how many times each code is recorded within CPRD and whether they are recorded in the Clinical, Referral or Test files.

The code list for each comorbidity was then reviewed by RP and AS. For some of the comorbidities, code lists had already been produced and validated within the department and were therefore used to maintain consistency. For example in the case of vascular disease (Clarson et al., 2013) and fractures. (Paskins et al., 2018) In these cases, code lists were produced for this thesis, but then compared to the existing lists. Any disagreements between them were reviewed and codes were either added or removed as appropriate. In the majority of cases however, due to the wide scope of this study and the large number of comorbidities, there were no existing lists.

Unlike PMR case ascertainment, prescription data was not used to provide confirmation of disease status. This was due to the large range of comorbidities and the heterogeneous way in which they could be treated. The accuracy of using CPRD Read codes for diagnosis has been demonstrated in a wide range of morbidities. (Khan, Harrison and Rose, 2010; Nissen et al., 2017) Furthermore, unlike in the case of PMR, many of these comorbidities, for example

hypertension, diabetes and asthma, have established diagnostic tests or criteria, therefore the use of prescription data to corroborate diagnostic status was not necessary.

2.12 Licensing

The Institute of Primary Care and Health Sciences at Keele University holds a General Practice Online Database (GOLD) licence to download CPRD data and it will be analysed using Stata software, version 15.1. (StataCorp, 2017)

2.13 Conclusion

The CPRD is therefore a valid, robust, database containing information gathered from a large population, during the course of routine primary care, who are representative of the population of the United Kingdom as a whole. It is the largest and most utilised verified primary care database in the UK and arguably the world. (Williams et al., 2012) PMR is most commonly managed in primary care. Therefore, the CPRD is the most robust data source for an accurate, real world estimate of the number of patients with this condition. The following chapter describes the epidemiological study performed to investigate the incidence and prevalence of PMR in the United Kingdom, using data from CPRD.

Chapter 3 AN EPIDEMIOLOGICAL STUDY OF THE INCIDENCE AND PREVALENCE OF POLYMYALGIA RHEUMATICA IN THE UNITED KINGDOM 1990-2015

This chapter is an epidemiological study of the incidence and prevalence of PMR in the UK in the period 1990-2015. This study will identify patients with PMR in primary care using the CPRD database.

3.1 Introduction

As discussed in chapter 1, existing estimates of the prevalence and incidence of PMR in patients aged over 50 years lie between 0.1-1% (C Salvarani et al., 1995; Hayward et al., 2014) and 12 - 113 per 100,000 person years, respectively. (Salvarani et al., 1991; Barraclough et al., 2008; Raheel et al., 2017) The proportion of patients with PMR has been shown to be strongly linked to geography; as latitude increases, so do PMR rates. (Buttgereit et al., 2016) The majority of cases of PMR (71-84%) are treated in primary care, (Barraclough et al., 2008; Yates et al., 2016) however much of the existing literature is based on secondary care hospital records. Therefore, the burden of disease may have been underestimated.

Smeeth, Cook, and Hall 2006 used primary care data to estimate the incidence of PMR in the UK, reporting an overall rate of 84 per 100,000 person years, which was increasing with time. However, the final year of data published in this study was 2001, therefore more contemporaneous estimates of national data are

needed to guide health service provision. The methods used by Smeeth, Cook, and Hall 2006 will be replicated in order to facilitate as accurate a comparison between the data as possible. The following chapter describes an investigation to quantify the overall incidence and prevalence of PMR in the UK using a large population-based database. This has been published as an extended report in the Annals of the Rheumatic Disease (appendix 3).

3.2 Methods

3.2.1 Data source and study population

This study was conducted using the CPRD, a large and robust database, which contains information collected in the course of routine primary care in the United Kingdom. The CPRD was described in detail in chapter 2.

3.2.2 Incidence

The study period chosen was between 1st January 1990 and 1st January 2016. This period represents the entire CPRD dataset from its inception to the time when the study was conducted, and represents a significant length of time to observe for trends in the incidence and prevalence of PMR.

In order to calculate the amount of data (time) that each patient contributed, individualised study start and end dates had to be defined. Each patient included in this study contributed data from the latest of five events: 1) the study start date, 2) the date at which they became forty years old, 3) the date they most recently registered at a participating practice plus six months, 4) the first registration date at a participating practice, or 5) the date at which the practice was adjudged to reach internal quality standards; known as the 'up-to-standard' date.

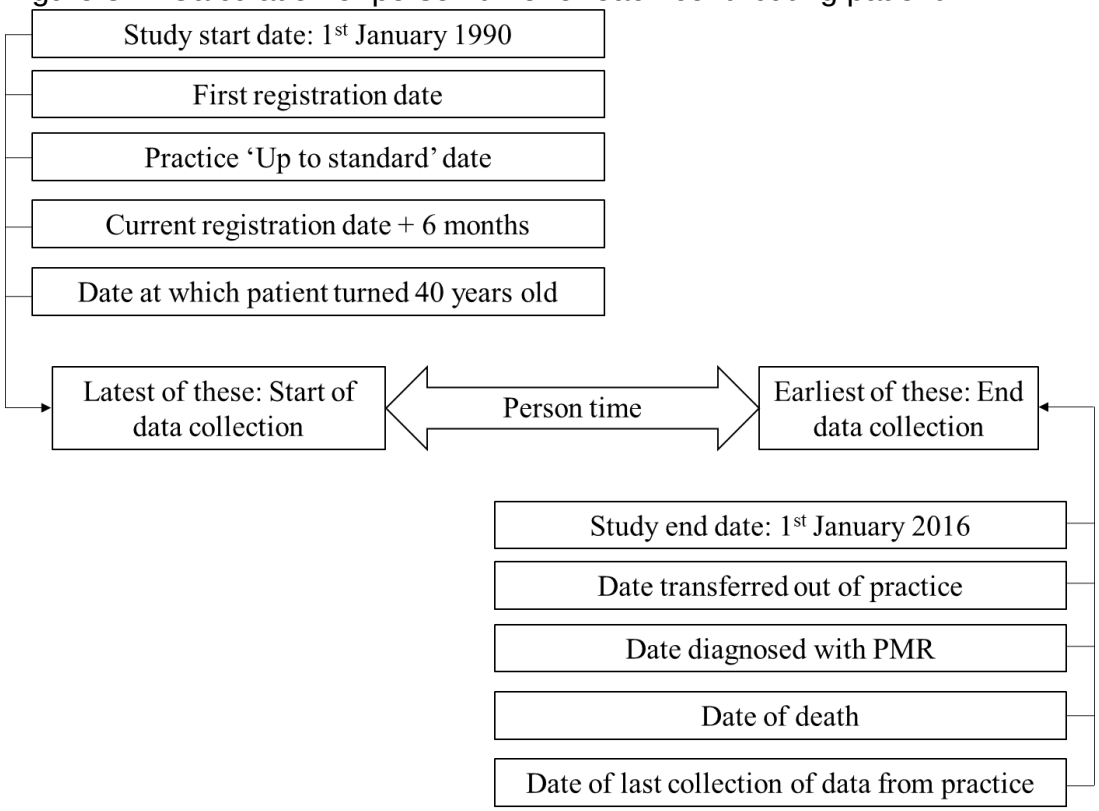
PMR is very rare in patients aged less than 50 years old, with a mean age of onset reported to be approximately 73 years. (Doran et al., 2002) Forty years of age was chosen as a cut off in order to replicate the earlier work of Smeeth et al. (Smeeth, Cook and Hall, 2006) The up-to-standard date was used to ensure that

the data being collected from the practice was of sufficient standard. Adding an additional six months to the most recent registration date with a practice ensured prevalent cases were not included in the analysis. When a patient registers with a GP practice, their medical history is transferred to the EHR system at their new host practice. When this happens, historic diagnoses can be incorrectly coded as occurring on the date of registration. (Wallace et al., 2015) Therefore, this data was excluded.

The date at which follow up ended for each patient was the earliest of five events: 1) the end of study period (1st of January 2016), 2) the date when a patient transferred out of a practice, 3) the date of a patient's death, 4) the last date of data collection from the practice, or 5) the date when they were diagnosed with PMR.

As previously discussed, PMR cases were identified when they were found to have a PMR Read code (codes: N20..00 Polymyalgia rheumatica, N200.00 Giant cell arteritis with polymyalgia rheumatica) in their EHR, as well as a record of at least two prescriptions for oral glucocorticoids; one within six months of the diagnosis date and the second within six months of the first prescription. Again, this follows methodology undertaken by Smeeth, Cook, and Hall 2006. Patients could have a diagnosis of both PMR and GCA. Only the first occurrence of PMR was included, therefore all subsequent person-time and diagnostic codes were excluded. This process, by which the amount of time each patient contributed to the study, is summarised in figure 3-1.

Figure 3-1: Calculation of person time for each contributing patient



3.2.3 Statistical analysis

As discussed in chapter 1, incidence is calculated by dividing the total number of new cases by the time total person years of follow-up. Because PMR is a relatively rare condition, the incidence rate was expressed per 100,000 person years. This is the same units as all but one of the existing studies into the incidence of PMR, promoting cross-study comparison. Incidence rates were stratified by age, sex, region and calendar year. Patient age was grouped into decades. Lexis expansion, which creates one observation per time interval per subject, (Hertz, 2001) was used to calculate incidence rates by year following the study start date of 1st January 1990.

A Poisson regression model was used to compare the absolute rate of PMR by patient characteristics and calculate incidence rate ratios (IRR) with 95% confidence intervals for each covariate, including sex, age, region and calendar year of diagnosis. Incidence rate ratios are, as the name suggests, ratios of two incidence rates. The calculation of an IRR for each covariate allows estimation of the increase, or decrease, in the risk of diagnosis with PMR that each covariate is responsible for.

Poisson regression is a form of regression analysis. It is used to calculate expected frequencies when the data follows the Poisson Distribution. The Poisson Distribution is a discrete probability distribution for the counts of events that occur randomly in a given interval of time. It is suitable for use when a number of criteria are satisfied: that the event can be counted in whole numbers, that occurrences are independent, that the average frequency for the time period in question is known and that it is possible to count how many times an event has occurred. Therefore, it is ideal to be used to describe the distribution of rare events in a large population.

The process of calculating an IRR involves obtaining the ratio of two incidence rates; the rate of the covariate in question and a reference rate. The reference rates for each group of covariates were taken from the same group to ensure subjects were not counted more than once. The rates used as the reference values for the covariates age, sex and region were the age band 50-59, males and patients resident in the North West of England respectively. The age range and region were chosen as they provided the greatest amount of person time. Males were chosen as the reference rate as the rate of PMR was higher in

females, therefore a more clinically relevant calculation was to obtain the increase in the risk of PMR diagnosis in females rather than the decrease in males.

Age-adjusted incidences for each sex, region and year were calculated using standardisation. There are two different methods for calculating standardised rates: direct and indirect. Direct standardisation involves the calculation of age-specific rates in each age group in the population and then applying these rates to weights from a standard population. Therefore, this is the theoretical rate which would have occurred if the observed age-specific rates applied in the standard population. Indirect standardisation involves the opposite approach, wherein the age specific rates of a known population are then applied to the number of people in each age group of the population of interest. (Naing, 2000)

Age specific rates were calculated in this study, therefore, direct standardisation was employed. As this study included only people aged over 40 years then commonly employed standard populations, such as the European standard, (Eurostat, 2013) were not appropriate. Therefore, the standard population in this study was the total population across the whole study period and, as discussed in section 2.7, the CPRD population distribution is similar to the wider UK population distribution.

In order to determine this, the total amount of person time each patient contributed to this study within each decade of age was calculated. This was calculated by using Lexis expansion (Hertz, 2001) to split the person time each patient contributed into decades following their date of birth. The amount of time that each patient contributed to the study in each decade of life was then totalled

and, finally, the overall value for each decade was converted to a proportion of the total person time (table 3-1).

Table 3-1: The proportion of person time per decade 1990-2016

Decade	Proportion of time
40	0.30
50	0.26
60	0.21
70	0.15
80	0.08
90	0.01
Total	1.00

Following this the crude incident rate, then the product and finally the expected incident rate for each decade was calculated thus:

$$crude\ incident\ rate\ (per\ 100{,}000\ person\ years\ per\ decade)$$

$$= \frac{number\ of\ events}{person\ time} * 100{,}000$$

$$product\ (per\ decade) = crude\ incidence\ rate * age\ proportion$$

$$expected\ incident\ rate = \sum products$$

3.2.4 Prevalence

The point prevalence of PMR was calculated for each calendar year. This was done by dividing the total number of patients who had received a diagnosis of PMR at any time in the past and were alive and contributing data on 31st December of that year (numerator) by the total number of patients alive and

contributing data on that date (denominator). Therefore, this enabled inclusion of both incident and prevalent cases.

3.2.5 Sensitivity analysis

A number of sensitivity analyses were performed to ensure the validity of the study findings. First, to investigate whether a large number of prevalent cases were included after the current registration date, the total number and rate of diagnoses of PMR were calculated during this period. (Wallace et al., 2015) Second, the incidence rates without GC prescriptions were calculated over the study period. Finally, comparisons were made between results from this study and previous studies of incidence and prevalence, by Smeeth, Cook, and Hall and Yates et al. respectively. In the case of prevalence comparison, the age threshold for this study was increased to 55 years and the results recalculated in order to allow direct comparison.

3.3 Results

3.3.1 Incidence

A total of 5,364,005 individuals contributed 43.97 million person-years of follow-up in the period 1990-2016. The total number of new occurrences of PMR that fulfilled the GC prescription criteria was 42,145. This equated to 90.4% of the total number of PMR cases recorded during this time. The overall incidence rate of PMR amongst patients aged 40 years and over was 95.9 [95% confidence interval (CI): 94.9, 96.8] per 100,000 person-years (table 3-2). Incidence rates were significantly higher at older ages: those aged over 70 years of age were almost ten times (IRR= 9.61 [95% CI 9.25, 9.98]) more likely to have PMR compared to those between the ages of 50 and 59 years. Females were 67% more likely to develop PMR compared to males (IRR= 1.67 [1.64-1.71]). A marked variation in incidence rates by region was found (figure 3-3), with rates highest in the south west region of the UK (124.1 [120.6-127.6]) and lowest in the north east (65.0 [59.5- 70.9]).

3.3.2 Prevalence of PMR

The point prevalence of PMR in 2015 among patients aged over 40 years was 0.85% (table 3-2) and was markedly different between males and females (0.6% and 1.16% respectively). This means that, given the UK population includes 32.8 million people aged over 40 years, approximately 280,000 people had received a diagnosis of PMR. As part of a sensitivity analysis, prevalence was found to

increase to 1.7% (95% CI 1.69%, 1.71%) when the threshold for inclusion in the study increased to only those patients aged over 55 years.

Table 3-2: Incidence rates of PMR, with incidence rate ratios, stratified by age, sex and region

	Number of events	Person time at risk *	Rate per 100,000 (95% Confidence Intervals)	Incidence Rate Ratio (95% Confidence Intervals) **	Age standardised Incidence Rate * ++
Overall	42,145	439.70	95.9 (94.9, 96.8)		
Age					
40-49	409	129.96	3.2 (2.9, 3.47)	0.11 (0.10, 0.13)	
50-59	3,139	113.75	27.6 (26.7, 28.6)	Reference	
60-69	9,683	91.62	105.7 (103.6, 107.8)	3.80 (3.65, 3.96)	
70-79	17,620	64.76	272.1 (268.1, 276.1)	9.61 (9.25, 9.98)	
80+	10,405	33.05	314.9 (308.9, 321)	10.58 (10.17, 11.13)	
Sex					
Male	13,651	212.06	64.4 (63.3, 65.5)	Reference	69.22
Female	28,494	227.64	125.2 (123.7, 126.6)	1.67 (1.64, 1.71)	114.87
Region					
North East	500	7.69	65 (59.5, 70.9)	0.82 (0.75, 0.90)	62.54
North West	3,843	49.36	77.9 (75.4, 80.4)	Reference	77.54
Yorkshire & the Humber	1,286	16.91	76.1 (72.0, 80.3)	0.97 (0.92, 1.04)	73.62
East Midlands	1,461	16.71	87.4 (83.1, 92.0)	1.14 (1.07, 1.21)	86.13
West Midlands	4,207	41.45	101.5 (98.5, 104.6)	1.26 (1.21, 1.32)	98.44
East of England	4,698	38.44	122.2 (118.8, 125.8)	1.56 (1.49, 1.62)	120.41
South West	4,850	39.10	124.1 (120.6, 127.6)	1.45 (1.39, 1.51)	112.96
South Central	4,754	46.70	101.8 (98.9, 104.7)	1.29 (1.24, 1.35)	101.57
London	2,901	40.63	71.4 (68.9, 74.1)	0.97 (0.93, 1.02)	75.76
South East Coast	5,167	43.89	117.7 (114.6, 121)	1.42 (1.36, 1.48)	110.23
Northern Ireland	991	13.76	72 (67.7, 76.6)	0.93 (0.87, 1.00)	73.06
Scotland	3,154	40.05	78.7 (76.0, 81.5)	1.03 (0.99, 1. 08)	81.51
Wales	4,333	45.01	96.3 (93.5, 99.2)	1.16 (1.11, 1.21)	90.05

*** Per 100,000 person years**
**** Adjusted for age, sex, region and year of diagnosis if not stratified as a covariate**
++ Incidence rate is adjusted by age using overall proportion of person time contributed per 10 year age category

3.3.3 Incidence of PMR over time

The variation in incidence rates of PMR over time are displayed in table 3-3 and figure 3-2. The rate of diagnosis of PMR dipped a little after 1990 until 1996 before increasing significantly until just after the end of the last century; after this the rate of diagnosis of PMR remained relatively stable between 2003 and 2014.

Table 3-3: Incidence rates of PMR by calendar year

Year	Number of events	Person years at risk (per 100,000 person years)	Rate per 100,000 person years (95% confidence interval)	Incidence Rate Ratio *	Age standard-ised Incidence Rate ++	Point prevalence
Overall	42,145	439.70	95.9 (94.9, 96.8)			0.84%
1990	261	3.30	79.2 (70.1, 89.4)	Reference	76.3	0.34%
1991	336	4.54	74 (66.5, 82.3)	0.91 (0.77, 1.07)	69.4	0.38%
1992	401	5.27	76.1 (69, 83.9)	0.94 (0.80, 1.09)	72.1	0.44%
1993	464	6.02	77.1 (70.4, 84.4)	0.95 (0.81, 1.10)	71.9	0.49%
1994	476	6.55	72.7 (66.5, 79.6)	0.90 (0.77, 1.04)	68.4	0.52%
1995	548	7.06	77.7 (71.4, 84.4)	0.96 (0.83, 1.11)	74	0.57%
1996	657	8.06	81.5 (75.5, 88)	1.01 (0.87, 1.16)	77.4	0.60%
1997	754	9.34	80.7 (75.2, 86.7)	1.01 (0.88, 1.17)	77.6	0.62%
1998	863	10.69	80.7 (75.5, 86.3)	1.01 (0.88, 1.16)	76.5	0.64%
1999	1,239	13.00	95.3 (90.1, 100.8)	1.20 (1.05, 1.38)	91.7	0.66%
2000	1,537	15.85	96.9 (92.2, 101.9)	1.23 (1.08, 1.40)	93.7	0.68%
2001	1,792	17.75	100.9 (96.4, 105.7)	1.28 (1.13, 1.46)	98.1	0.71%
2002	2,131	20.05	106.3 (101.9, 110.9)	1.36 (1.20, 1.55)	103.5	0.74%
2003	2,211	21.49	102.9 (98.7, 107.3)	1.33 (1.17, 1.51)	101.4	0.77%
2004	2,296	22.96	100 (96, 104.2)	1.30 (1.15, 1.48)	98.5	0.79%
2005	2,348	23.73	99 (95, 103)	1.30 (1.14, 1.48)	98	0.80%
2006	2,389	24.12	99.1 (95.2, 103.1)	1.30 (1.15, 1.48)	97.7	0.83%
2007	2,451	24.45	100.3 (96.4, 104.3)	1.32 (1.16, 1.50)	99.7	0.83%
2008	2,495	24.60	101.4 (97.5, 105.5)	1.33 (1.17, 1.51)	100.7	0.85%
2009	2,447	24.64	99.3 (95.5, 103.3)	1.30 (1.15, 1.48)	98.2	0.85%
2010	2,497	24.34	102.6 (98.6, 106.7)	1.35 (1.19, 1.53)	101.6	0.86%
2011	2,379	23.83	99.8 (95.9, 103.9)	1.32 (1.16, 1.50)	99.1	0.87%
2012	2,268	23.50	96.5 (92.6, 100.6)	1.28 (1.12, 1.45)	95.9	0.87%
2013	2,198	22.51	97.6 (93.6, 101.8)	1.29 (1.14, 1.47)	96.8	0.88%
2014	2,037	20.58	99 (94.8, 103.4)	1.30 (1.14, 1.48)	97.2	0.88%
2015	1,603	17.60	91.1 (86.7, 95.6)	1.20 (1.05, 1.36)	89.1	0.85%

* adjusted for region, age, sex

++ Incidence rate is adjusted by age using overall proportion of person time contributed per 10 year age band

Figure 3-2: Overall, male and female incidence of PMR 1990-2015 with 95% Confidence Intervals

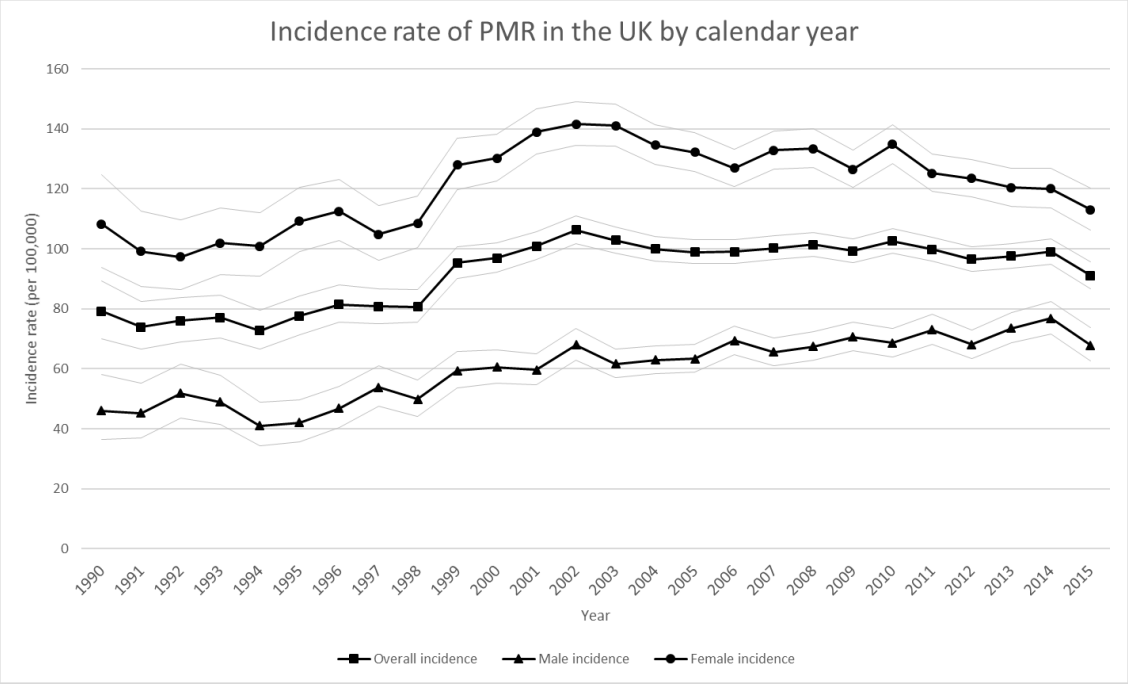
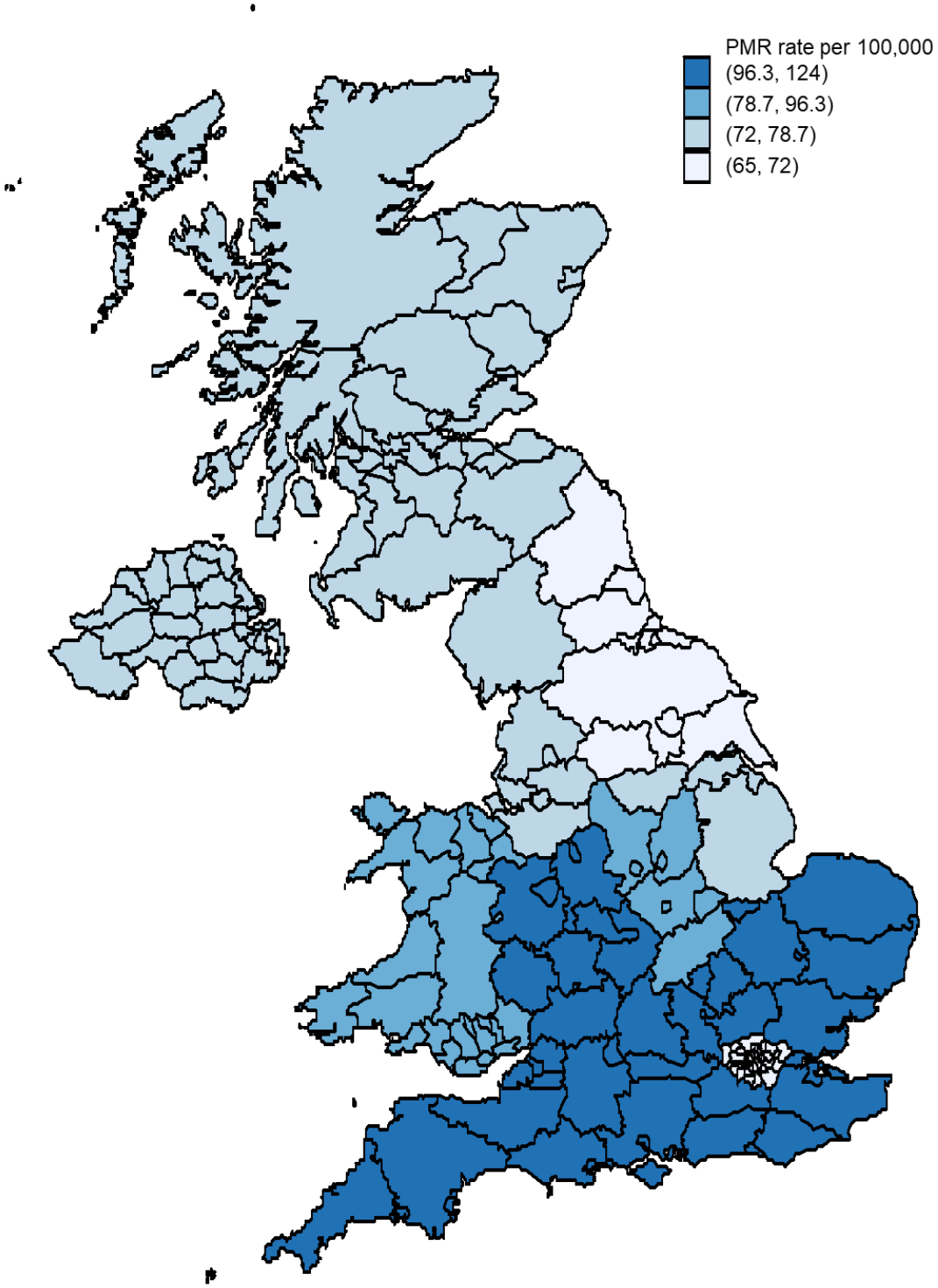


Figure 3-3: Incidence rates of PMR by region 1990-2016



3.3.4 Sensitivity analysis

The first sensitivity analysis confirmed that during the first six months after current registration date there was an excess of PMR diagnoses. This was apparent in a number of measurements following this date, including the absolute number of new diagnoses per year (figure 3-4) and per month, (figure 3-5) as well as the rate of new diagnoses per year (figure 3-6).

Figure 3-4: Total number of new diagnoses of PMR following current registration date (years)

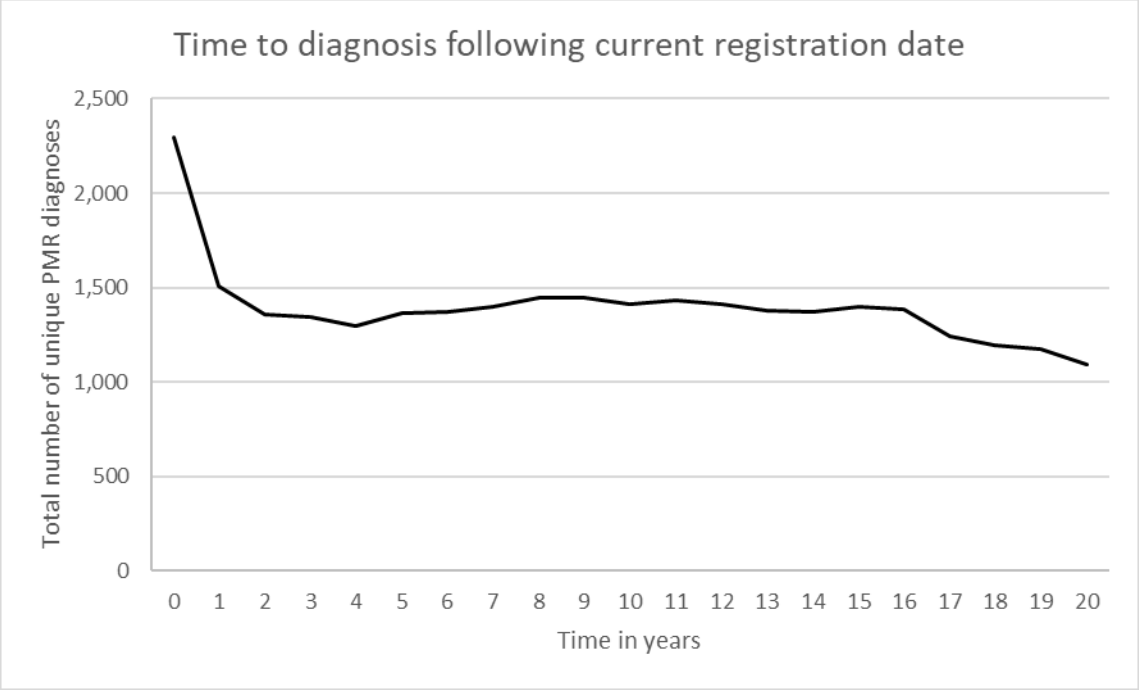


Figure 3-5: Total number of new diagnoses of PMR following current registration date (months)

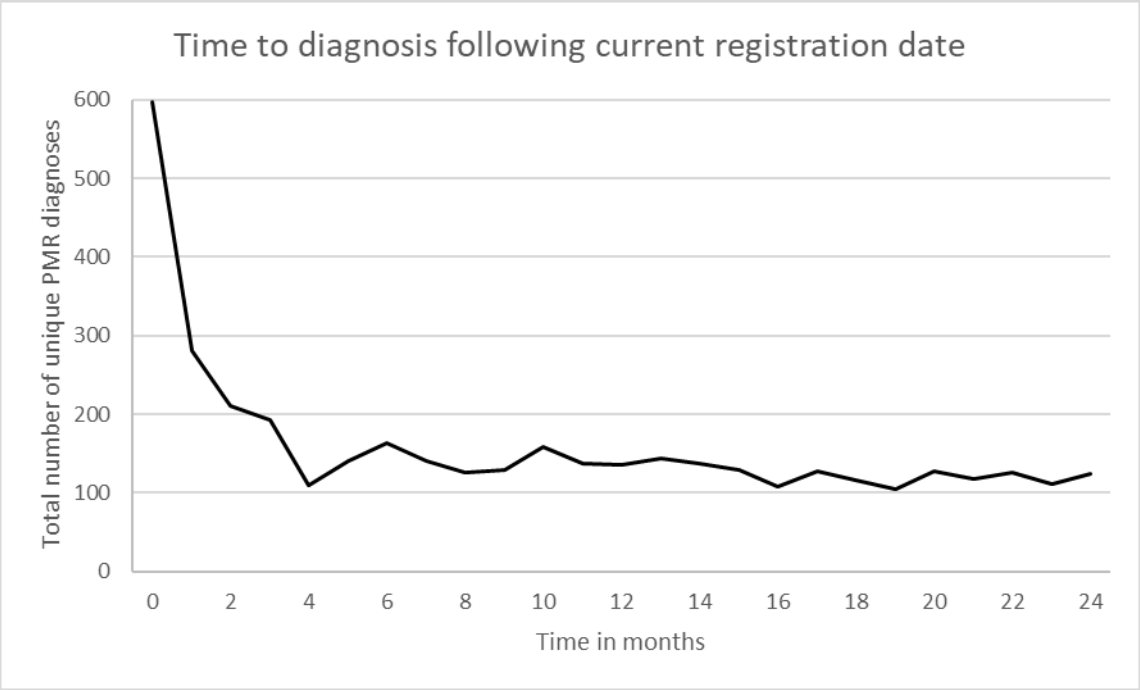
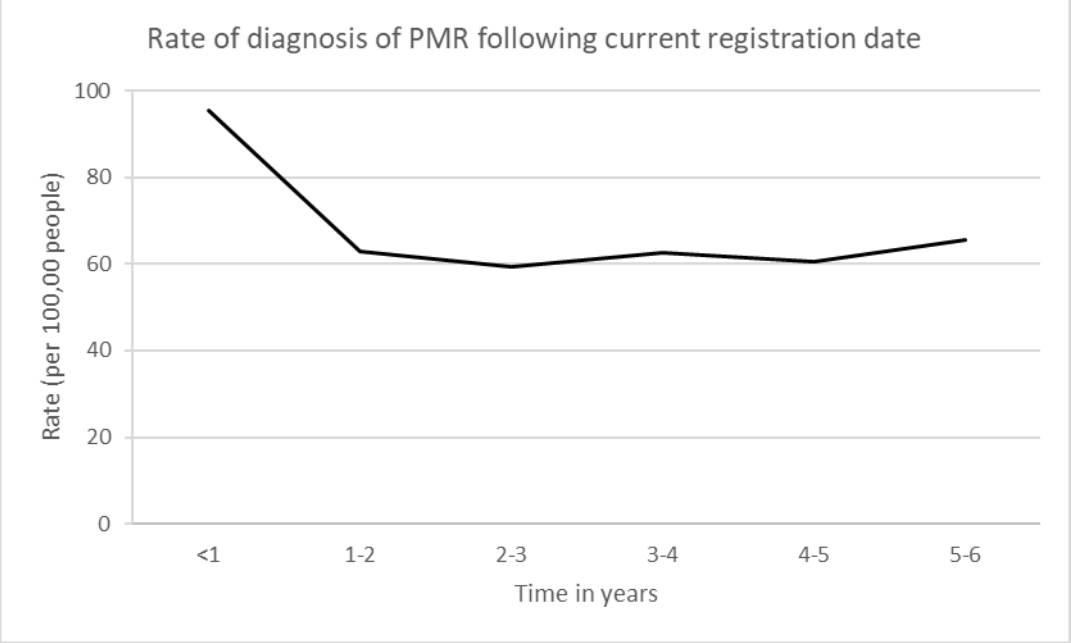


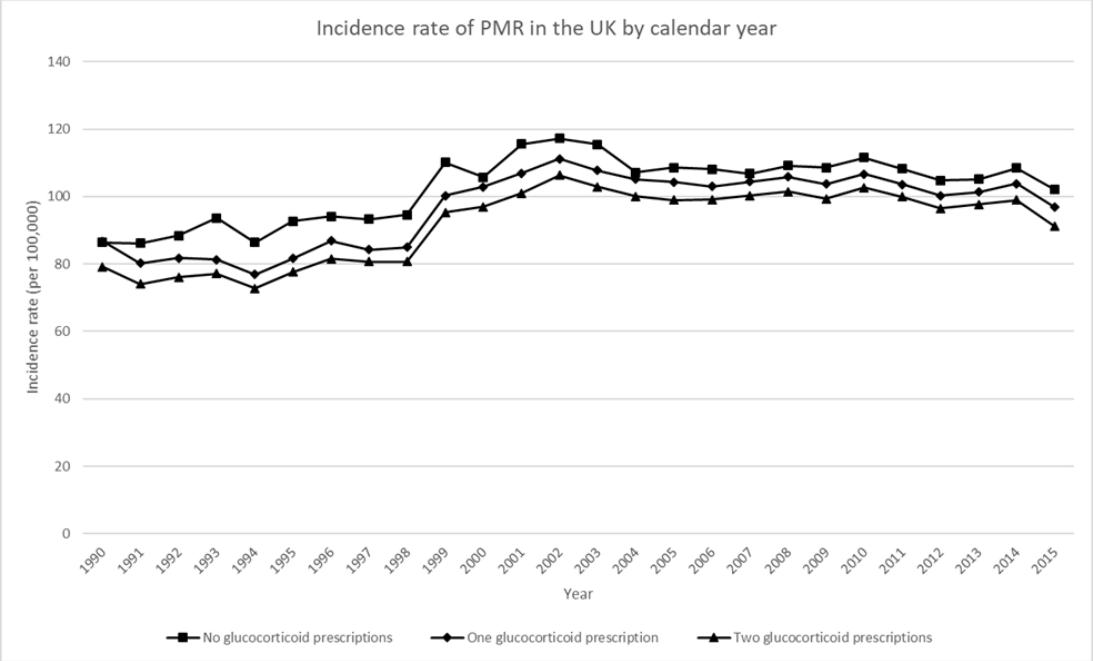
Figure 3-6: Incidence rate of new diagnoses of PMR following current registration date (years)



The second part of the sensitivity analysis involved assessing whether using glucocorticoids as part of the inclusion criteria reduced the rate of PMR diagnosis

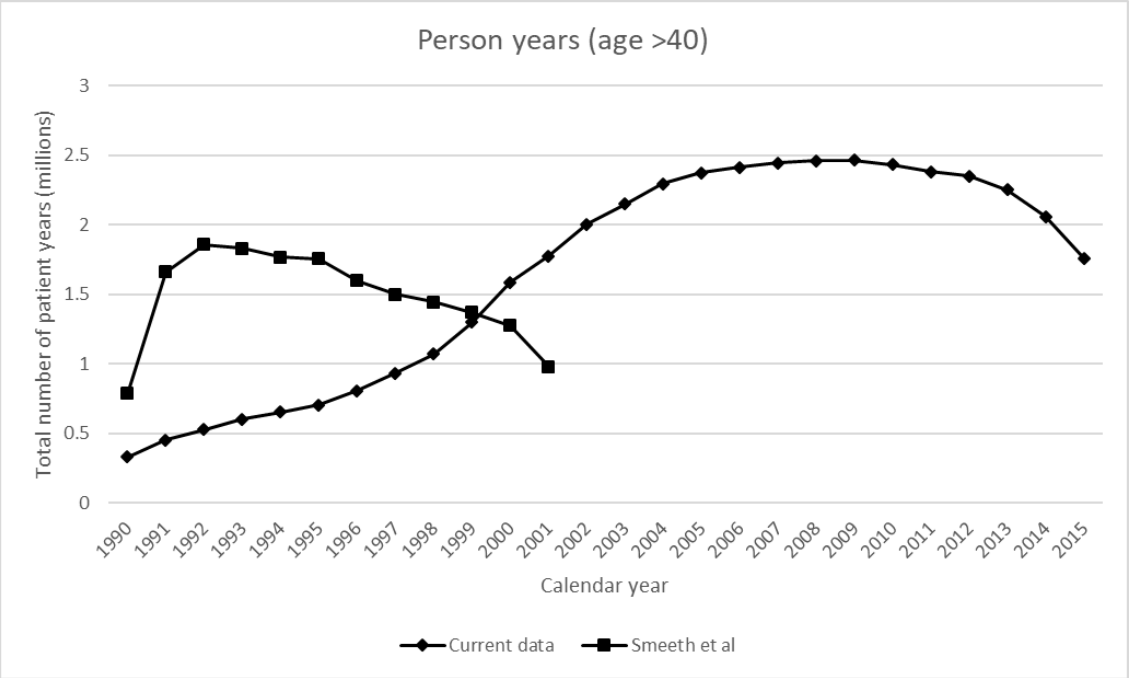
significantly. Over 90% of patients with a diagnosis of PMR had two GC prescriptions. The overall trend over time remained similar when the requirement for two prescriptions was reduced to only one or omitted entirely (figure 3-7).

Figure 3-7: Comparison of incidence rates when using different GC inclusion criteria



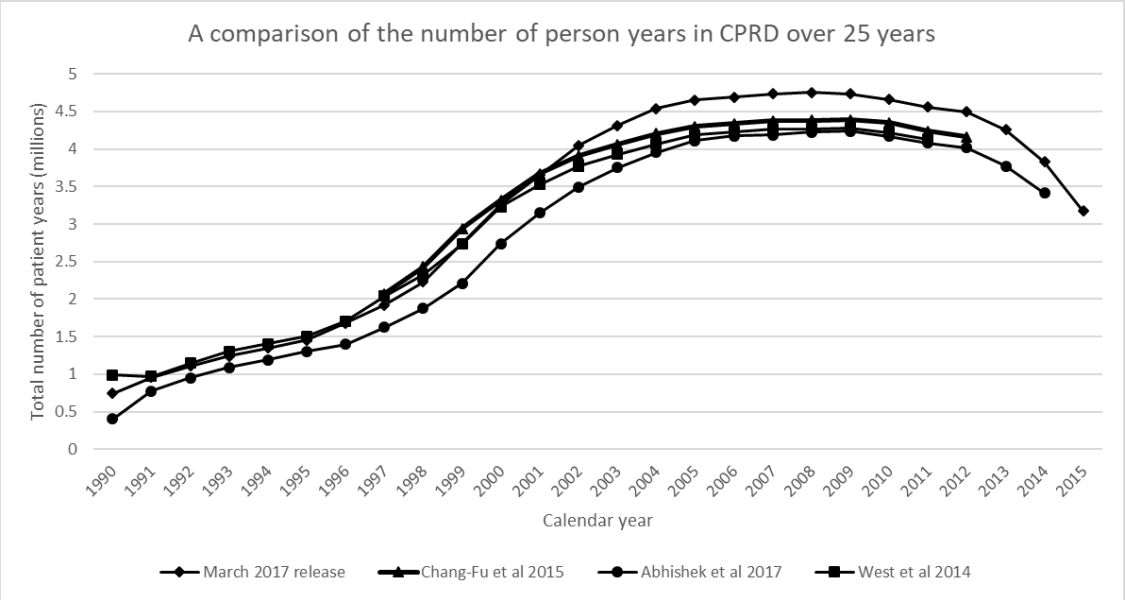
Finally, as part of the sensitivity analysis, the total number of person years in the current study and in the most recent similar study of PMR incidence by Smeeth, Cook, and Hall 2006 were compared. This is important, as the person years act as the denominator in the calculation of incidence. Although the inclusion criteria used in this study were almost the same in both studies, there were significant differences in the number of person years available between the two studies (figure 3-8).

Figure 3-8: Contributing person years over time in current CPRD database compared to previously reported data



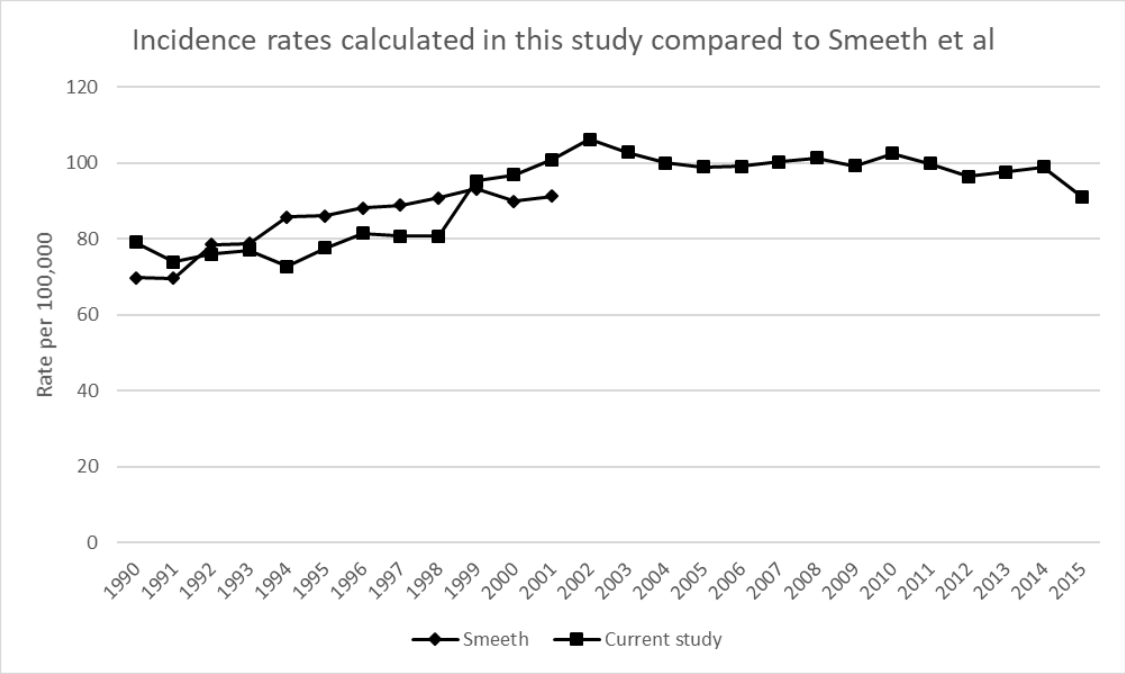
However, when the amount of person time available in this study was compared to three more recent CPRD studies, (West et al., 2014; Kuo et al., 2015; Abhishek et al., 2017) the amount of person time available for use as the denominator correlated much more closely (figure 3-9).

Figure 3-9: A comparison of person years available in recent CPRD studies of disease incidence



Although the number of person years in Smeeth, Cook, and Hall 2006 was different, the incidence rates reported by them were similar to that reported in the current study (figure 3-10).

Figure 3-10: A comparison of incidence rates of PMR in this study and previously reported by Smeeth et al



3.4 Discussion

3.4.1 Main findings

This study estimates the burden of PMR in the UK to be slightly higher than previously estimated. In 2015, around one in 120 adults aged over 40 had received a diagnosis of PMR, which, across the whole population, equates to approximately 280,000 people in the UK. Overall, the incidence of PMR during the study period 1990 to 2016 was 95.9 per 100,000 person years [94.9, 96.8]. However, although it increased until 2002, the incidence rate of PMR has stabilised after this time.

3.4.2 Strengths and limitations

This was the largest study ever conducted to calculate a true estimate of the incidence and prevalence of PMR. This study used robust methodology that has been replicated from previous studies in a large, established database of patients who are representative of the UK population. A limitation of this study could be that it only used primary care data. However, as discussed previously, the vast majority of patients are managed in primary care. (Barraclough et al., 2008; Yates et al., 2016) As well as this, in the UK, diagnoses made in secondary care are communicated to, coded and then recorded in the primary care EHR. Therefore, although this study examined patients in primary care, it will also contain information from treatment in secondary care. Therefore, the CPRD is the most appropriate setting to capture and accurately estimate the incidence and prevalence of PMR.

The accuracy of this study was increased by excluding prevalent cases by omitting the first six months of follow up after patients registered with a practice contributing to CPRD. This ensured only included newly incident cases were included when calculating rates, thus avoiding an over-estimate of the number of cases.

However, the method of case ascertainment could be regarded as a potential limitation. In this study, the diagnosis of PMR was based on medical codes recorded by the primary care physicians, rather than research classification criteria. (Dasgupta et al., 2012) One reason for this was that there wasn't sufficient consultation detail in CPRD to allow it. Patients may therefore subsequently be diagnosed with an alternative condition. However, it was found that more than 90% of patients with a diagnosis of PMR received at least two GC prescriptions. Furthermore, the rate of diagnosis was assessed in each year during the study period, and was found to be very similar even when prescription data requirements were varied or omitted entirely (figure 3-7). Finally, the use of GC prescriptions to confirm PMR diagnosis is well established and has been used by several studies previously. (Smeeth, Cook and Hall, 2006; Pujades-Rodriguez et al., 2016)

3.4.3 Comparison to other studies

The highest incidence, 113 per 100,000 patients, previously reported was a study from the south west of England. (Hayward et al., 2014) Although the overall incidence rate for the whole of the UK in the current study was lower than this,

the estimate for this region was slightly higher (124.1 [120.6, 127.6]). In the United States, the most recent estimates of PMR incidence reported by Raheel et al was 63.9 per 100,000. This is lower than the findings in this study. However, Raheel et al's study was not conducted in primary care and stricter diagnostic criteria, rather than diagnostic codes and record of GC treatment were used as inclusion criteria. (Raheel S, Crowson CS, 2016)

Employing less strict diagnostic criteria may not necessarily be a weakness of the current study. PMR can present in a range of different ways and using stricter inclusion criteria may lead to the exclusion of those with atypical presentations or other comorbid diseases. Ensuring all those who were labelled and treated for PMR are included means an accurate estimate of the burden of disease that PMR places on the UK healthcare system can be reached. Furthermore, the clinical classification criteria for PMR are designed for recruitment into research studies, not clinical practise.

As well as this, the study from Raheel et al was carried out in the United States, and was therefore based in a healthcare system that is structurally very different to that in the UK. In the UK, as previously discussed, access to healthcare is free and universal, however in the US it is estimated that up to 20% of working age people do not have health insurance, limiting access to healthcare (Okoro et al., 2015) Therefore, epidemiological research in the US may not be able to include a complete cross section of the population. Finally, whilst it can be argued that the definition of PMR used in the current study is not ideal, the estimated rates calculated were broadly in line with other studies that have used clinical classification criteria. Therefore the risk of misclassification is minimal.

Women were more likely to develop PMR, with a female to male ratio of approximately 2:1, reflecting previous studies. (e.g. Smeeth, Cook, and Hall 2006) The strong association between older age and risk of developing PMR has been demonstrated before, with other studies reporting median age at diagnosis of 70 (Yates et al., 2016) or 75 years. (Barraclough et al., 2008) As rates of frailty, aches, pains, (Buckinx et al., 2015) and ESR levels (Moghadam-Kia and Werth, 2010) increase with age, it is possible that primary care physicians may over diagnose PMR in at least some of these patients.

The prevalence of PMR has been found to vary between 0.1% and 1% in North Europe and North America. (Eaton et al., 2010; Hayward et al., 2014) The prevalence of 0.85% in 2015 calculated in our study is consistent with this. In a recent study in a single large GP practice in the south of the UK, (Yates et al., 2016) reported a prevalence of 2.27% in those aged 55 years and over. In the current study, when the exclusion criteria for age was likewise increased to all those under the age of 55, the prevalence increased to 1.7%. This discrepancy could be explained by the higher incidence of PMR in the south and east of the UK as well as the fact it utilised a much smaller sample of only 5,000 people.

Given PMR is known to preferentially affect people of northern European descent, the results of this study are likely to be generalisable to countries with a significant proportion of people from this ethnic group. However, results reported in this study are less generalisable to countries at lower latitudes, as incidence and prevalence rates have been found to reduce with decreasing latitude. (C Salvarani et al., 1995; Gonzalez-Gay et al., 1999, 2009)

The incidence of PMR appears higher in the south of the UK compared to the north. This was also demonstrated by Smeeth et al. (Smeeth, Cook and Hall, 2006) As discussed in chapter 1.2, genetic associations between specific Human Leukocyte Antigen molecules and GCA have been found, (Carmona et al., 2015) although none yet for PMR. (González-Gay, Matteson and Castañeda, 2017) A degree of variation in the genetic make-up of people in different regions around the UK has been demonstrated in a recent study of over 2,000 UK residents. (Leslie et al., 2015) This study was the first fine-scale dissection of subtle levels of genetic variation within a country, but did not examine the region of the genome which encodes for Human Leucocyte Antigens (HLA), as the genetic samples used in this study were obtained from patients with multiple sclerosis, a disease with strong HLA associations. As this is the area of the genome in which associations with GCA have been found, further analysis of genetic variation in HLA allele frequency in the UK may be required to be certain that genetic variation is not the cause of the variability in PMR incidence. However, if the genes for HLA vary in a similar manner to the rest of the genome, then it is unlikely that genetics are the reason for the difference in incidence of PMR, as the minor genetic variations observed by Leslie et al did not match with the changes in PMR incidence rates demonstrated in this study.

Other potential reasons could include an association between social class and PMR, retirement of elderly people to the south of the UK, a viral aetiological agent, or environmental differences such as less sunlight exposure in the north of the UK leading to reduced vitamin D levels and vitamin D deficiency being diagnosed preferentially to PMR. One previous study assessed the link between social class and PMR diagnosis. (Hayward et al., 2014) It did not find a link

between PMR diagnosis and socioeconomic status, which was based upon occupation, educational level and perceived adequacy of income. However, this study only assessed respondents within a small region of the UK, which limits its generalisability.

Smeeth, Cook, and Hall (2006) found that the incidence of PMR in the UK was increasing until 2001. This finding was replicated in the current study. After 2001 however, the incidence rate plateaued. Although the incidence rates reported were similar, there were differences in the amount of person time available to act as denominator between this study and Smeeth et al's work. In the current study, there was significantly more person-time available in the time period covered by Smeeth et al, compared their study.

This difference was due to gradual changes in the way that data has been collected by CPRD through its existence, and Smeeth et al's data was based on a much earlier version of CPRD data (Full Feature-GPRD). The main differences were around the "up-to-standard" and "current registration" dates. In the earlier versions of CPRD, the "up-to-standard" date was calculated once for each practice and remained the same after this. Now, it is calculated monthly based upon the data that is being collected at that time. Second, the "current registration date" was not included at all in earlier versions of CPRD, only the "first registration date". Therefore patients could contribute to the database even if they had periods of time in their records where they were not registered with that practice. Therefore, the current methods employed by CPRD to define when patients can contribute data, including the use of "up-to-standard" and "current registration

dates" provide for much more accurate data collection and account for the differences seen when compared to earlier versions of CPRD.

3.4.4 Conclusion and clinical implications

In conclusion, analysis of high quality routinely collected primary care data has enabled confirmation of the number of patients in the UK who are affected by PMR. Due to the ageing population, the prevalence of PMR in the UK is increasing, and in 2015 approximately 280,000 adults over 40 in the UK have received a diagnosis of PMR, although incidence rates appear to have stabilised. Therefore, a significant proportion of the UK population are affected by this important and potentially disabling condition.

The treatment of PMR is well recognised but there are persisting concerns that a large proportion of patients are subject to prolonged GC therapy. The next chapter will aim to answer the question as to whether a proportion of patients receive prolonged GC therapy by assessing GC prescribing among the PMR cohort identified in this study.

Chapter 4 AN EPIDEMIOLOGICAL STUDY OF THE TREATMENT OF PMR IN THE UNITED KINGDOM 1990-2015

This chapter is an epidemiological study of the management of PMR in the UK in the period 1990-2015. It will assess prescribing in patients with PMR in primary care using the CPRD database.

4.1 Introduction

In the UK, as described in chapter 3, polymyalgia rheumatica (PMR) occurs at a rate of 95.9 [95% confidence interval (CI): 94.9, 96.8] per 100,000 person-years, and 0.85% of people aged over 40 had received a diagnosis of PMR by 2015. This means around 280,000 people are currently, or have been, affected by this condition.

The management of PMR is well established. Joint guidance released by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) advises glucocorticoid (GC) treatment at moderate to low doses which, for most patients, should end by approximately two years. (Dejaco, Singh, Perel, et al., 2015; Buttgereit et al., 2016) This guidance was based on the results of a systematic literature review as well as taking current clinical practice into account. However, the authors acknowledged there was insufficient data to make evidence-based recommendations for all conceivable subgroups of patients with PMR. (Dejaco, Singh, Perel, et al., 2015) Furthermore, it has been suggested a large proportion of patients experience symptom flare upon cessation, or during GC therapy tapering (a “symptom tail’). (Mackie et al., 2014)

Long term GC therapy is associated with a number of significant adverse effects, (Moghadam-Kia and Werth, 2010) which are both dose (Huscher et al., 2009) and duration (Walsh et al., 2001) dependent. These adverse events, or complications, comprise a wide range of conditions; for example hypertension, obesity, cardiovascular disease, type two diabetes, cataracts, osteoporosis and proximal myopathy. (Moghadam-Kia and Werth, 2010) As such, the treatment for PMR also encompasses the prevention and management of the potential complications associated with GCs. These complications are not only common, they can also significantly impair patients' health and functional status. Furthermore, GC therapy side effects are a key concern of patients with PMR. (Tshimologo et al., 2018)

The aim of this study is to quantify prescribing of GCs in those diagnosed with PMR using a large, population-based, database.

4.2 Methods

The cohort of 42,145 patients, identified in chapter 3, was used for this study. The methods used to identify these patients were explained in the previous chapter.

All GC prescriptions that were recorded in CPRD for these patients after their date of diagnosis, or index date, using medications from BNF chapter 6.3.2 “Glucocorticoid therapy”, (Royal Pharmaceutical Society, 2017) were included in the main analysis. The GCs prescriptions used in the analysis included prednisolone, deflacort, dexamethasone, hydrocortisone, methylprednisolone and triamcinolone. As previously discussed, all GC prescriptions that were orally or parenterally administered were included and topical preparations were excluded. All GC prescriptions were then converted to a strength equivalent to prednisolone using the BNF glucocorticoid conversion calculator. (Royal Pharmaceutical Society, 2017) For example, a prescription for 20mg hydrocortisone is regarded as equivalent to 5mg of prednisolone.

CPRD contains information about quantity of medication prescribed, the number of units of medication to be taken each day (numeric daily dose) and prescription duration. However, this information is not always complete, as it may be recorded in the EHR using free text, rather than a Read code. For example, in GC prescriptions where a ‘reducing regime is required’ then the phrase ‘as directed’ may be coded, with more specific instructions inputted as free text on the EHR.

In order to solve this issue, researchers have used a variety of methods in previous studies of GC prescribing. For example, one recent study opted to use

“defined daily doses”, produced by the World Health Organisation, which are the average maintenance dose of a drug per day when used for its main indication in adults. (World Health Organisation, 2018)

For this study, however, the method used to calculate duration of GC therapy was adapted from that used in a previous study of GC related adverse events. (Paskins et al., 2018) Using this method, the duration recorded for a prescription, if present in CPRD, was used in the first instance. If duration data was not available, then either the quantity prescribed, or the number to be taken per day, or the gap to the next prescription were used, in that order, to calculate the duration. If it was still not possible to calculate a duration at this time, then either the average duration of other similar prescriptions for that patient was used, or if this was not available, the average duration for that prescription in all patients. The method is summarised in the algorithm shown below (figure 4-1).

Figure 4-1: Algorithm for calculating GC prescription length

1. If available, duration of each prescription recorded in CPRD was used.
2. If not, the duration of each prescription was the lowest of,
    a. the quantity of medication prescribed; or
    b. the gap until the next prescription (if this was <90days); or
    c. the quantity of medication prescribed divided by the daily dose (if this was recorded).
3. If the duration was still missing, it was replaced with,
    a. the average of that patient's duration for other prescriptions of the same drug with the same strength (if present); or
    b. the average duration for all other patients' prescriptions of the same drug with the same strength.
4. If prescription duration was >90 days, it was replaced as 90 days.
5. The total duration was calculated as the sum of all prescription durations for each patient.

The primary outcome measure was duration of time from diagnosis, or index date, until completion of continuous GC therapy. Kaplan-Meier survival methods were used to calculate the median duration of time from diagnosis until completion of continuous GC therapy. (Kaplan and Meier, 1958) The Kaplan-Meier estimator is a nonparametric statistic used to estimate survival from lifetime data. Nonparametric statistics refer to a statistical method where the data is not required to fit a normal distribution.

A Kaplan-Meier analysis allows estimation of survival over time, even when patients join or leave a study at different times. At each interval, the probability of

survival, in this case continuation of GC therapy, was calculated. Patients who have died, transferred to a different practice, or left the study for any other reason were not counted as part of the denominator, or censored, after the time point when they left the study.

The end of a treatment course was determined to have occurred when no further GC prescriptions occurred for 90 days after the calculated duration of the previous prescription. The 90-day period was chosen as it is the same as in previous CPRD based studies of medication use. (Vinogradova et al., 2016)

The date of diagnosis with PMR, or index date, was the start date of the study for each patient. The date at which each follow up ended was the earliest of five events: 1) the end of study period (1st of January 2016), 2) the date when a patient transferred out of a practice, 3) the date of a patient's death, 4) the last date of data collection from the practice, or 5) the date when continuous GC treatment ended.

Further analyses carried out included extending the period of time defined as end of treatment from 90 days to six months and then until end of all GC therapy for that patient. This was to specifically examine patients who underwent multiple courses of GC therapy and assessed whether extending the length of time allowed between prescriptions led to an increase in total continuous treatment time.

4.2.1 Sensitivity Analysis

For further analysis of treatment patterns, the average daily and total dose of GC prescribed, as well as cumulative treatment time and the total number of prescriptions and separate treatment courses each patient received were calculated. Dosage calculations were made, as discussed in section 2.10, by converting the strength of all medications to milligrams of prednisolone equivalent using the BNF conversion tables of equivalent anti-inflammatory doses. (Royal Pharmaceutical Society, 2017) Results were further stratified by starting GC dose, age and sex.

The average and total dose, as well as total duration, of GC therapy were also calculated and compared to ascertain whether any association was seen between these variables. For example if a longer duration of therapy was associated with an increased total GC dose received.

Two further analyses were carried out where the duration of prescriptions were recalculated. The first involved categorising separately patients who received a diagnosis with another rheumatological condition, either prior to PMR diagnosis, or in the two years subsequently. PMR guidelines suggest that the presence of other rheumatological conditions would preclude a diagnosis with PMR, and that treatment of PMR should end by two years following diagnosis, then this was an appropriate duration to include. Other rheumatological diagnoses were identified using Read code lists developed for a comorbidity study described in chapter 6.2.7. Patients who received another rheumatological diagnosis could be at risk of prolonged GC therapy.

The second analysis involved categorising separately those patients who were subsequently referred to secondary care rheumatology services after index date. These patients were identified using Read codes. Patients who were referred to secondary care could represent atypical, or more severe, presentations of PMR analyses. Therefore, due to them potentially having more serious diseases, they may also be subject to longer treatment durations.

Finally, the distribution of all GC prescriptions, including those made prior to index date was also assessed to investigate whether patients with PMR are prescribed GCs prior to a formal diagnosis being made. This analysis was performed to investigate to what extent GCs were used as a therapeutic trial prior to diagnosis. A therapeutic trial refers to a situation in which patients with non-specific symptoms are prescribed GCs and then monitored for a response. In this case, if the symptoms and inflammatory markers improve, then a diagnosis of PMR may then be made. Previous research has shown this is a diagnostic approach viewed as important in PMR. (Helliwell et al., 2018)

4.3 Results

4.3.1 Main findings

In total 1,242,841 GC prescriptions were issued to patients with a diagnosis of PMR. Of these prescriptions, 99.9% contained information about quantity of medication prescribed, and 48.3% about numeric daily dose. The median time taken for patients to stop continuous therapy was 1.31 years [Interquartile range [IQR] 0.65, 2.6] (figure 4-2). When the treatment gap was increased to six months, the median duration increased to 1.88 years [0.93, 4.00]. When total GC treatment time was reviewed, median duration increased further to 1.93 years [0.95, 4.03], meaning around 25% of patients received more than four years of therapy (figure 4-3).

Figure 4-2: Kaplan-Meier plot of time to completion of GC therapy (90 day period)

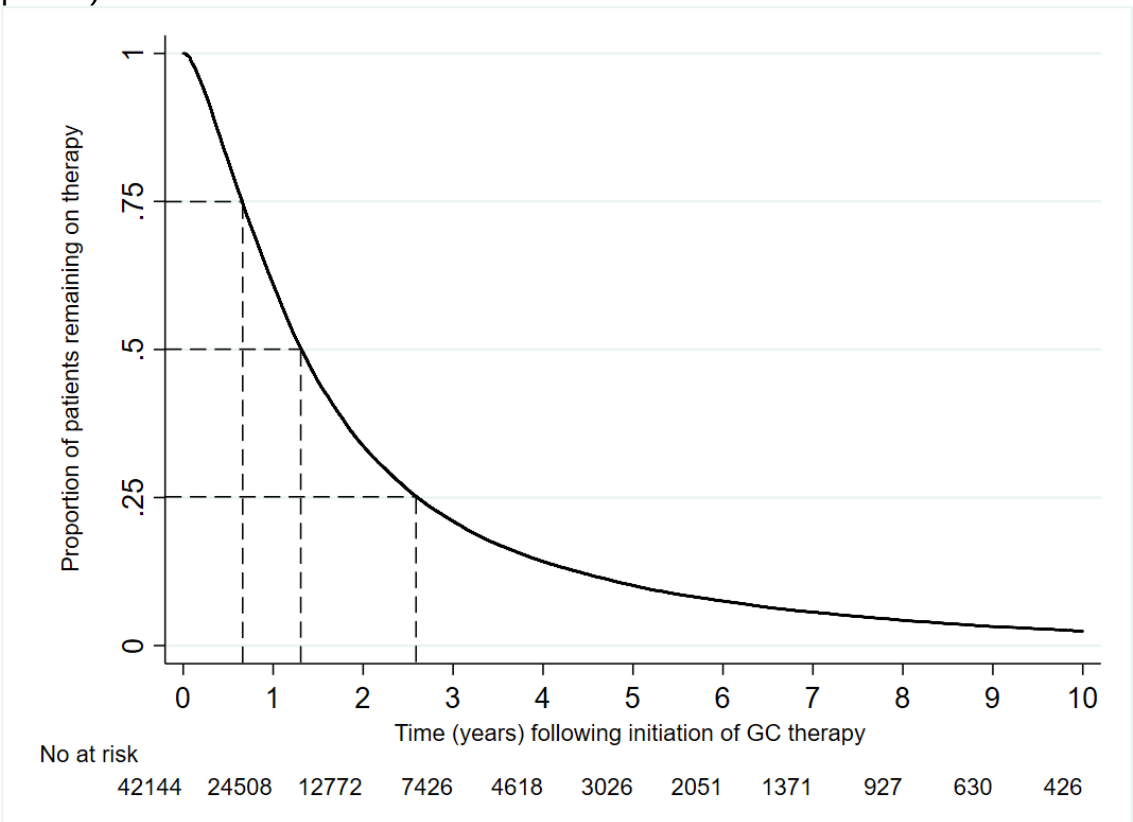
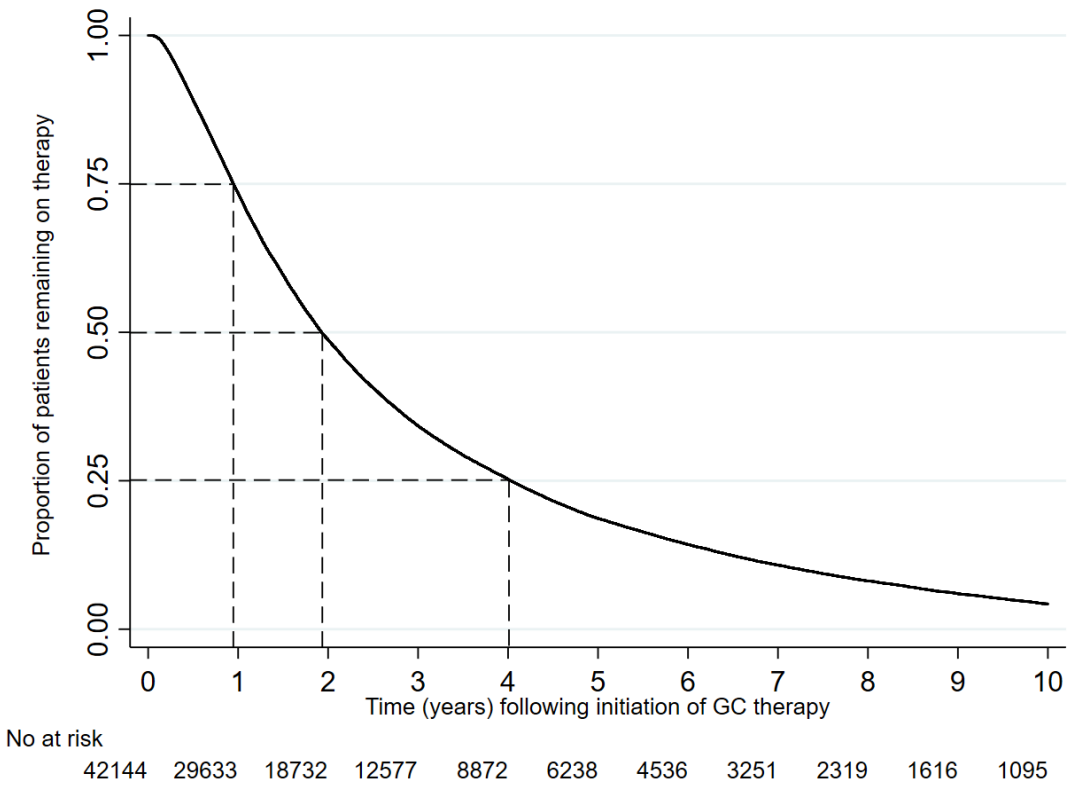


Figure 4-3: Kaplan-Meier plot of time to completion of GC therapy



4.3.2 Sensitivity analysis

The median first and average daily doses of GC received (in milligrams of prednisolone equivalent) were 15mg [IQR 8, 21] and 6mg [IQR 4, 9] (figure 4-4) respectively. However, 7,138 (16.9%) patients received, on average, greater than 10mg GC per day. The median total dose of GC received (in grams of prednisolone equivalent) was 4g [IQR 2, 8] (figure 4-5). The distribution of average daily doses was positively skewed, reflecting the fact that the mean average daily dose which patients received (7.4mg [Standard deviation [SD] 4.9]) was higher than the median.

Repeating analyses stratified by initial GC dose, age and sex was unremarkable, with only patients aged under 50 receiving significantly fewer prescriptions.

Figure 4-4: Average daily dose of GC in patients with PMR

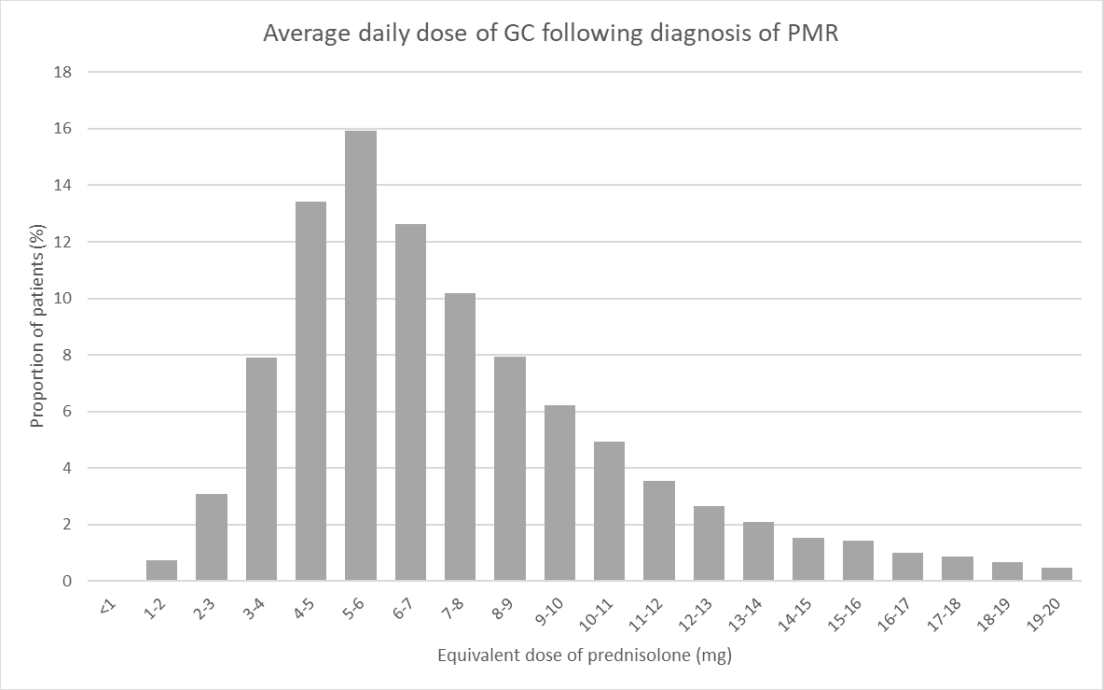
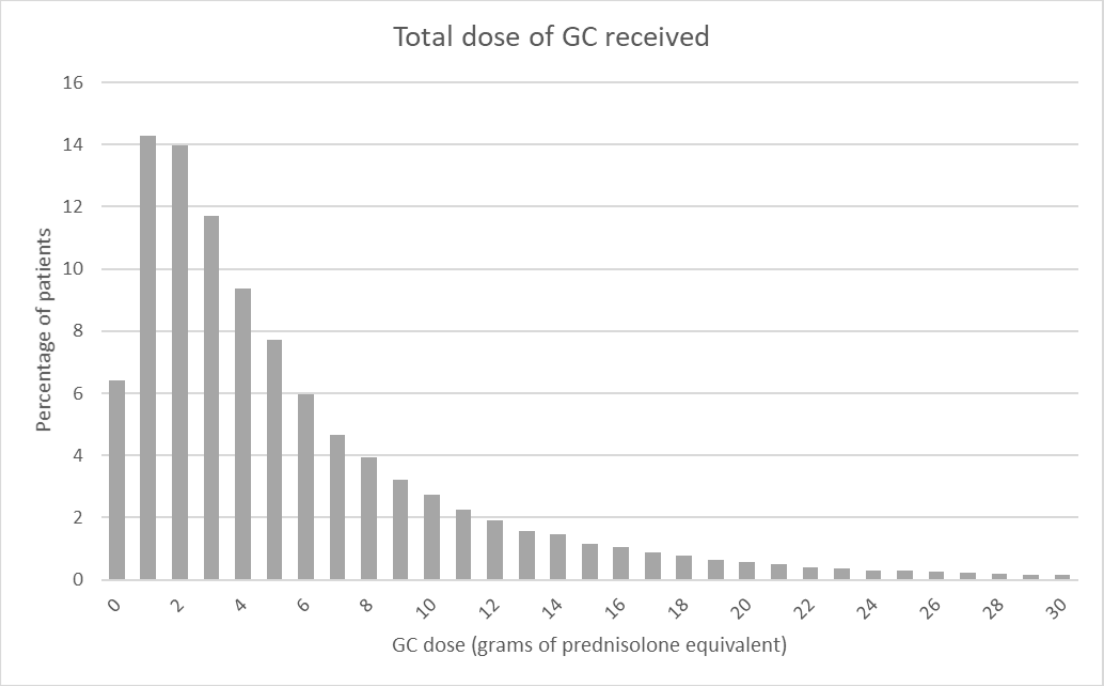


Figure 4-5: Total dose of GC received by patients with a diagnosis of PMR



The next phase of analysis involved assessing whether an association existed between cumulative treatment time and average daily GC dose, (figure 4-6)

cumulative treatment time and total dose received, (figure 4-7) or total dose received and average daily dose (figure 4-8).

Figure 4-6: Scatter plot showing relationship between average daily GC dose prescribed and duration of GC therapy

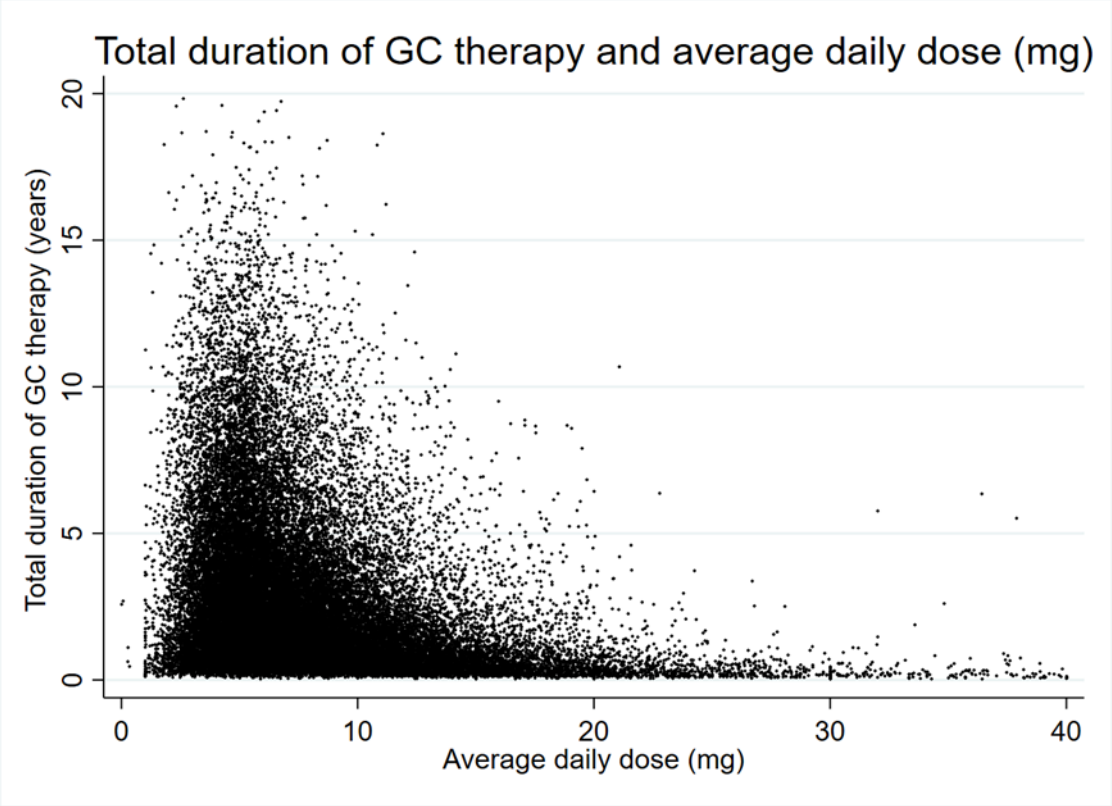


Figure 4-7: Scatter plot with linear regression line showing relationship between total GC dose prescribed and duration of GC therapy

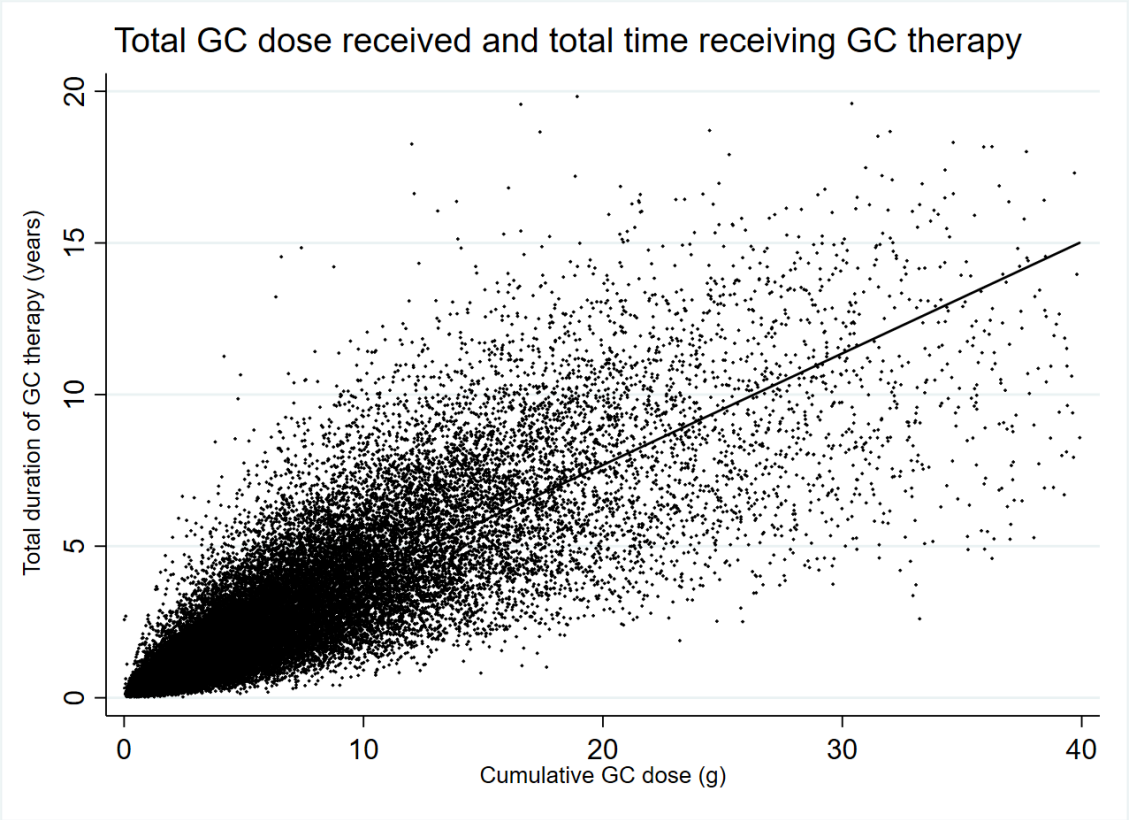
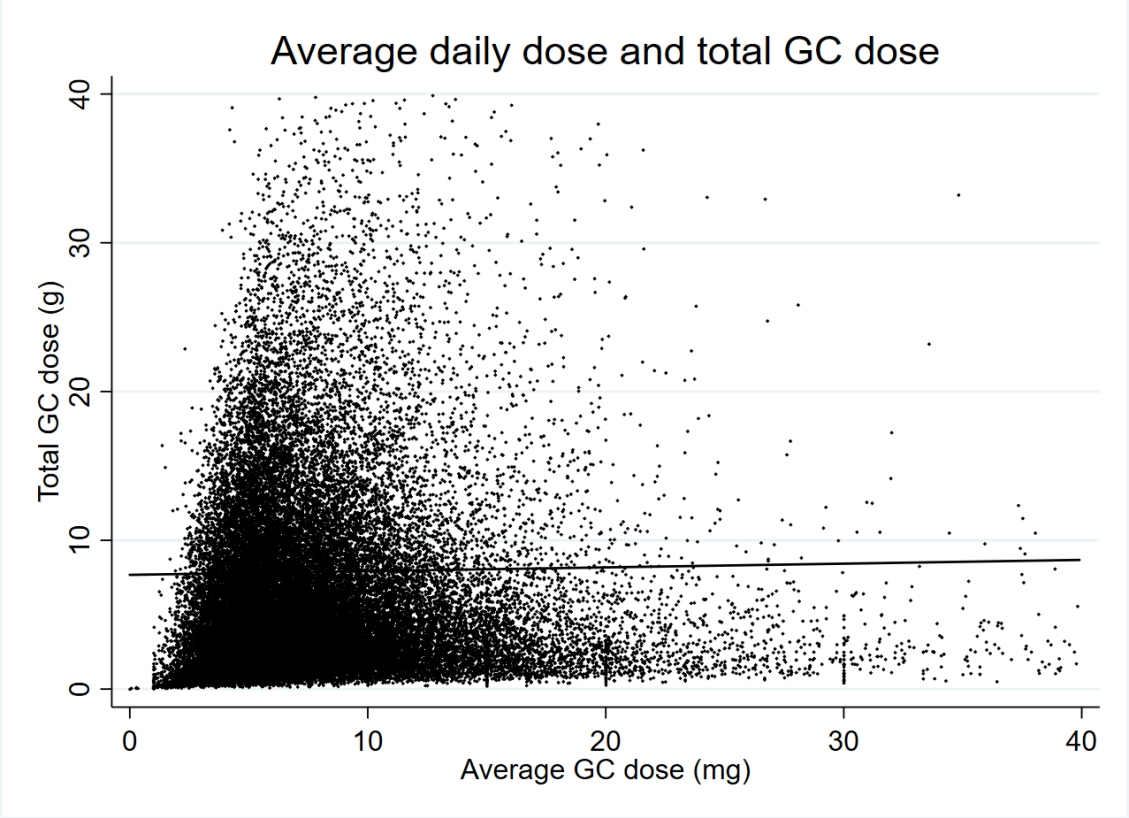


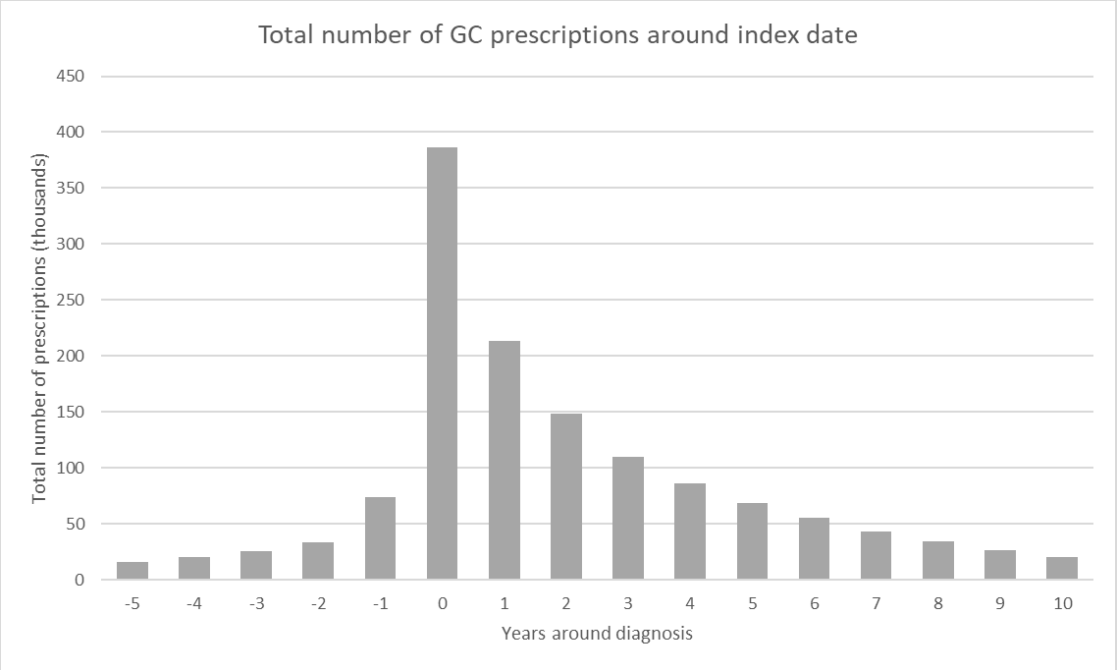
Figure 4-8: Scatter plot with linear regression line showing relationship between total GC dose prescribed and average daily GC dose



As is seen in figures 4-6 and 4-8, no association was seen when looking at the average daily dose of GC that a patient received compared to either the total GC dose received, or duration of GC therapy. However, demonstrated by the linear prediction line which was calculated from a linear regression, strong association existed between total dose of GC therapy received and duration of treatment (figure 4-7).

The distribution of GC prescriptions around index date demonstrated that the absolute number of GC prescriptions began to increase prior to the index date (figure 4-9).

Figure 4-9: Total number of GC prescriptions around index date



The final part of the sensitivity analysis involved ascertaining whether GC prescription length was longer in patients who either had a coexistent rheumatology diagnosis or those who had been referred to rheumatology. In

these situations it was found that the median continual duration of GC therapy was indeed greater, at 1.49 [0.73, 3.16] (figure 4-10) and 1.55 years [IQR 0.79, 3.06] (figure 4-11) respectively.

Figure 4-10: Kaplan-Meier plot of time to completion of GC therapy (90 day period) in patients with another coexistent rheumatological diagnosis

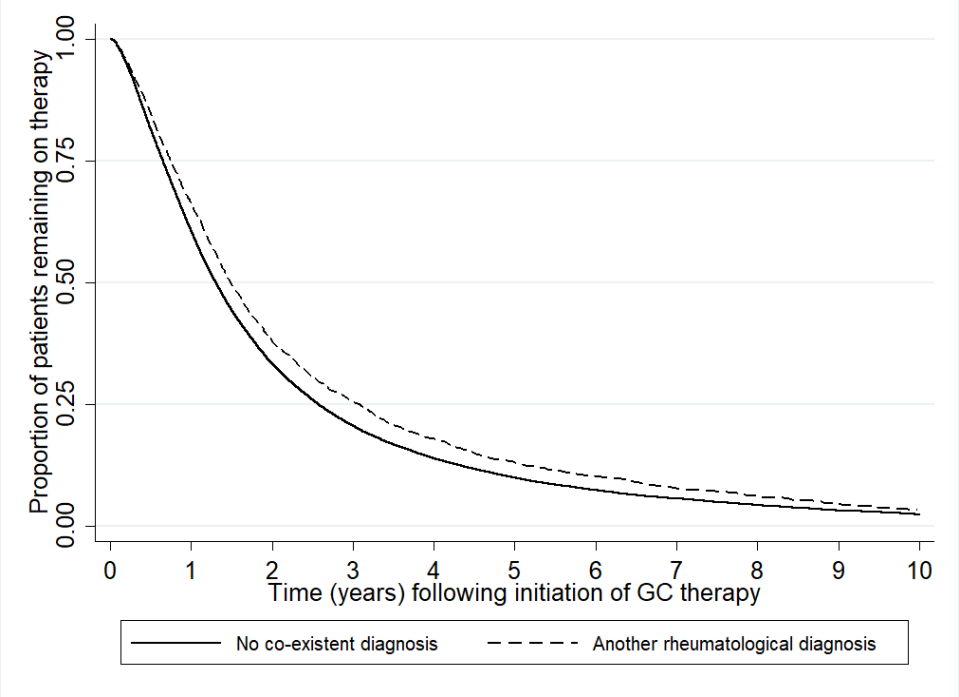
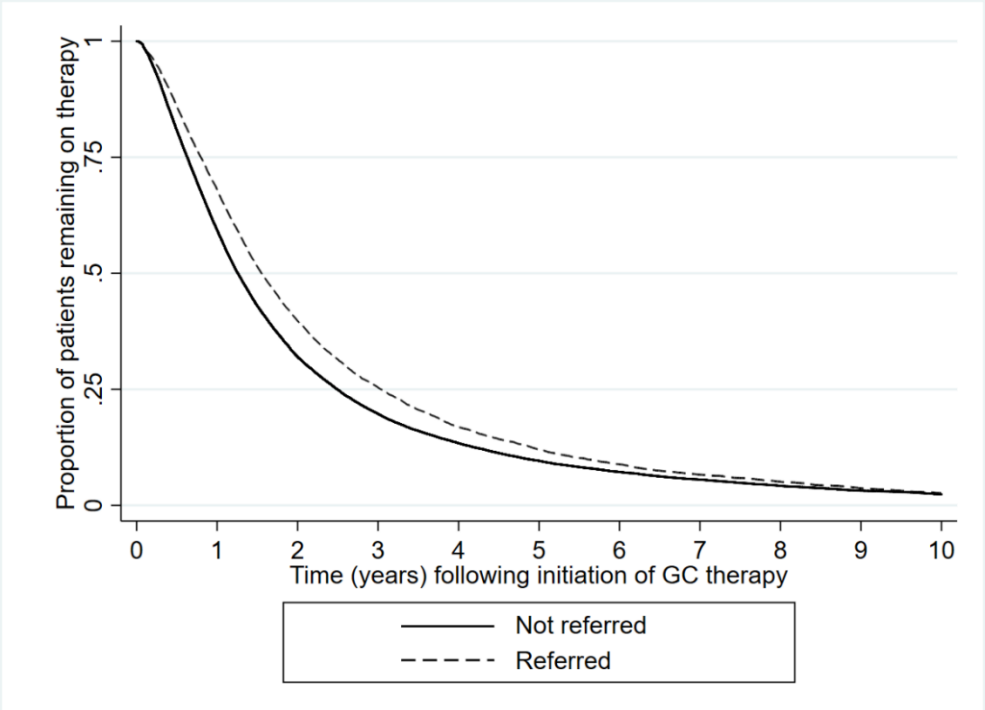


Figure 4-11: Kaplan-Meier plot of time to completion of GC therapy (90 day period) in patients referred to secondary care



4.4 Discussion

4.4.1 Main findings

Analysis of high quality routinely collected primary care data has confirmed that a significant proportion of patients with PMR receive prolonged treatment with GCs. The median time taken for patients to stop continuous therapy was 1.31 years [Interquartile range [IQR] 0.65, 2.6] and the median total length of treatment was 1.93 years [0.95, 4.03]. This means that almost 25% of patients with a diagnosis of PMR received more than four years of GC therapy.

4.4.2 Strengths and limitations

This is the largest study yet to calculate a true estimate of the current treatment patterns of patients with PMR. The methodology is robust and the study was conducted in an established database that is representative of the UK population. The methods used for calculating GC duration and dose were robust and have been used in previously published work. (Paskins et al., 2018) Furthermore, as indicated before, most patients with PMR are managed exclusively in primary care. (Barraclough et al., 2008; Yates et al., 2016) Therefore, this is an appropriate place in which to perform this study.

Cases were identified using Read codes and GC prescriptions, rather than clinical classification criteria. This method is well established and allows identification and analysis of treatment patterns for very large numbers of people diagnosed with PMR in routine clinical practice outside of the confines of

research studies. This gives a unique insight into real life medicine and what happens in current GP practice, compared to what guidelines suggest. Furthermore, as more than 90% of patients in this study received at least two GC prescriptions, the diagnosis of PMR is likely to be accurate for the majority of patients.

Of the 1,242,841 GC prescriptions that were issued to the patients in this cohort, 99.9% contained information about quantity of medication prescribed, and 48.3% about numeric daily dose. The almost universal capture of the number of medications issued per prescription was expected, given the way that prescriptions are generated by EHRs. However, around half of the prescriptions did not contain data on numeric daily dose, i.e. how many to take per day. This is perhaps to be expected given the long duration of GC therapy and the necessity for individualised regimens and patient self-management of GC reduction. For example, if the daily instructions were either ‘as directed’ (asd), or different doses on alternate days, or the patient was on an individualised reducing regime, then this data would not be available for CPRD.

The algorithm to calculate the length of prescriptions, as well as other data such as average daily dose and total dose, was therefore important when data was missing. This algorithm was described in detail in chapter 4.2. All prescriptions were assumed to be for a maximum of 90 days. This methodology was in line with previous CPRD studies of duration of treatment in other conditions. (Vinogradova et al., 2016) It is likely, however, that this algorithm slightly underestimated the overall duration of treatment.

4.4.3 Comparison to other studies

The initial GC dose patients received was between 8-21mg in 50% of patients, which corresponds well to the recommended starting dose of 12.5-25mg. (Dejaco, Singh, Perel, et al., 2015) Less than one fifth of patients (18.3%) received greater than 25mg. However, the median duration of treatment of patients with GC in this sample is less than that found by Shbeeb et al in their recent study into GC prescribing in a cohort of 359 patients with PMR in Olmsted County, Minnesota. (Shbeeb et al., 2018a) They found only 19% of patients discontinued therapy in the first year of their treatment compared to 27% in this study. However, the median dose prescribed in each study was similar, at around 5-6mg.

A number of reasons for the shorter treatment duration in the current study are possible. For example, in Shbeeb et al's study, the patient sample may represent more severe variants of the condition, as their inclusion criteria were stricter. To be included in their study, and other Olmsted county reports of PMR, patients had to fulfil three criteria, 1) age 50 years or older; 2) bilateral aching and morning stiffness (lasting ≥ 30 min) persisting for at least 1 month and involving 2 of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs; and 3) erythrocyte sedimentation rate elevated to > 40. (Doran et al., 2002) Introducing symptom and laboratory criteria mean it is likely that the number of patients included will reduce and that they may have more severe disease.

Furthermore, there were methodological differences in the definition of the end of GC therapy. The main analysis in the current study used a gap of 90 days to

define completion of therapy. However, in Shbeeb et al's work, the total length of therapy was used. In a sensitivity analysis, when the total duration of therapy was assessed, the median length of treatment increased to 1.93 years [Interquartile Range [IQR] 0.95, 4.03]. This means that one in four patients with PMR in the UK are subject to treatment with GC therapy for more than four years.

There are several potential explanations for a prolonged symptom tail. It could in part represent a more severe subtype of PMR that requires more aggressive and prolonged treatment. Some of this group may actually have a different underlying GC responsive diagnosis, for example elderly onset rheumatoid arthritis, for which referral for secondary care review may be appropriate. Alternatively, it may represent GCs masking the symptoms of other inter-current comorbidities which flare upon reduction of GC treatment, or adrenal insufficiency following prolonged GC use.

4.4.4 Sensitivity analyses

Patients who subsequently received a referral to a secondary care rheumatological services and those with a coexistent rheumatological diagnosis both had on average longer durations of GC therapy. These patients are likely to represent people with PMR where there is uncertainty around diagnosis or a more severe subtype of PMR. Additionally, guidance advises that patients who require treatment in excess of two years should be referred for rheumatological review, (Dejaco, Singh, P, et al., 2015) and so it is unsurprising that this was found.

Graphs displaying the average daily, and total, dose of GC received took the form of positively skewed normal distributions with a mean average daily dose of 7.4mg [Standard deviation [SD] 2.9], which was greater than the median average daily dose of 6mg [IQR 4, 9]. This provides further evidence for the existence of a group of patients who receive significantly higher doses of GC compared to guidelines.

The total number of GC prescriptions received unsurprisingly peaked in the first year following diagnosis (index date) and reduced rapidly in the first two years following this before continuing to reduce at a lower rate. However, the absolute number of GC prescriptions actually began to increase the year before formal diagnosis was made. This is likely to be due to the non-specific signs that are characteristic of PMR. In these cases it may be that GPs are using GCs as part of the diagnostic pathway, in effect a 'trial of treatment', wherein patients with signs atypical to PMR are given GC therapy and subsequently coded as PMR if they improve with treatment.

It was found that the average daily dose of GC therapy received was not associated with either duration of treatment or total GC dose received. However, as could be expected, the total dose of GC received was well associated with duration of treatment. This finding is perhaps unsurprising, that patients who received prolonged GC treatment will receive higher doses of glucocorticoids, but drives home the importance of identifying these patients at an early stage in their treatment journey. If identified at an early stage, these patients who are at risk of prolonged therapy and therefore higher overall doses of GC, could either then be

referred for consideration of disease modifying anti-rheumatic drugs (DMARDs), or be monitored and treated more intensively for GC related complications.

4.4.5 Clinical relevance

Previous studies have shown that long-term GC treatment increases a person's risk of a wide range of complications. (Moghadam-Kia and Werth, 2010) The risk of complications due to GC therapy have been divided into those which exhibit a linear, and those with a dose threshold, relationship. Complications with a linear relationship, in which the risk of a complication increases gradually with an increased daily GC dose, include bruising, leg oedema, thin skin, and sleep disturbance. A dose threshold relationship is where the risk of a complication remains relatively low until the daily dose exceeds a certain threshold, after which it increases greatly. Examples of complications and the threshold doses include >5mg/day: cataracts, 5-7.5mg/day: epistaxis and weight gain, >7.5mg/day: depression, glaucoma and hypertension. (Huscher et al., 2009)

Therefore, this study has made an important and clinically relevant discovery that a significant proportion of patients receive a high total dose of GC over a prolonged length of time. The next steps from this point are to attempt to discover the subgroups who are at high risk of prolonged, large GC doses.

Why some patients are treated with higher doses of GCs may be due to variations in treatment regimens within regions. For example, in Bristol (UK), local rheumatologists and GPs created a rapid access diagnostic care pathway to identify and treat patients with PMR. Their treatment guidelines specified the use

of prednisolone at doses of 15mg per day for six weeks, followed by 12.5mg for the next six weeks and then 10mg for one year, prior to instituting a reducing regime of 1mg/month thereafter. (Quick and Kirwan, 2012) This may be particularly relevant to this study given the higher incidence of PMR in the southwest of England. Furthermore, this variation in treatment again emphasises that, although treatment guidelines exist, it is acknowledged there aren't evidence-based recommendations for all subgroups of patients with PMR. (Dejaco, Singh, Perel, et al., 2015) This highlights a need for future research to create formal treatment and tapering regimes for all patients with PMR.

4.4.6 Conclusion

A significant proportion of patients with PMR receive prolonged treatment with, and therefore higher doses of, glucocorticoids. This is contrary to previously held beliefs that cure will typically be achieved within two years. Early identification of patients who are likely to be subject to prolonged GC therapy is a priority area for future research. These patients could then be fast-tracked to secondary care for consideration of GC-sparing agents. This research could take the form of detailed prospective observational cohort trials in which patients with suspected PMR are identified and clinically examined in detail to attempt to ascertain which factors present, if any, predispose people to an increased likelihood of prolonged therapy.

This study, in a large population, confirms the existence of a prolonged 'symptom tail' in PMR; wherein a significant number of patients receive a higher average

daily dose, a larger total dose, more individual prescriptions of GC and receive their treatment over a longer period of time.

The current incidence, prevalence and treatment patterns of patients with PMR have thus been established. It is now important to assess the overall health of patients with PMR. It is not clear whether patients with PMR have worse health than other patients of their age. If this is the case, this may influence the likelihood of patients being subject to prolonged treatment with GCs and exposure to the resultant increased risks of complications. The first step in this process is to conduct a systematic review of existing evidence of the frequency of comorbidities, which are present both before, and subsequently develop after diagnosis of, PMR.

The following chapter describes a systematic review of literature in this area.

Chapter 5 COMORBIDITIES IN POLYMYALGIA RHEUMATICA: A SYSTEMATIC REVIEW

This chapter is a systematic review of published literature around comorbidities present before and after diagnosis with PMR.

5.1 Introduction

In the two previous chapters, the incidence, prevalence and treatment of polymyalgia rheumatica, was determined using a general practice electronic record database. However, little is known of the overall health of patients with PMR before and after their diagnosis. The presence of multiple co-existent, or comorbid, diseases are common in the general population. (Barnett et al., 2012) It is not clear whether patients with PMR have a similar or different pattern of comorbidity than the general population.

It is well established that patients with certain inflammatory rheumatological conditions are predisposed to developing cardiovascular disease (CVD), for example gout (Clarson et al., 2013) and rheumatoid arthritis (RA) (Avina-Zubieta et al., 2012). In patients with RA, this risk has been attributed to an increased prevalence of arterial atherosclerotic plaques, (Jonsson et al., 2001; Pamuk, Ünlü and Çakir, 2006) the quantity of which are correlated with levels of systemic inflammation, (Kumeda et al., 2002) as well as the duration of rheumatological disease. (Dessein et al., 2007) Patients with RA are also known to have a higher risk of lung diseases, (Brown, 2007) and certain types of cancers, particularly haematological malignancies. (Chen et al., 2011)

PMR shares many traits with RA - they are both rheumatological conditions characterised by increased levels of inflammation. Therefore, it is important to ascertain whether patients with PMR have a similar predisposition to an increased risk of certain conditions.

Establishing whether patients with PMR are at a higher risk of certain comorbidities is even more significant given the clinical classification criteria produced to guide diagnosis of PMR. These guidelines, which are endorsed by the American College of Rheumatology and the European League Against Rheumatism, advise that in order to diagnose PMR the presence of other conditions that may cause similar symptoms must be excluded. (Dejaco, Singh, Perel, et al., 2015) Unfortunately, due to the wide range of symptoms, (especially in early presentation) and non-specific signs and investigations that are a part of PMR diagnosis, this list of potential conditions to exclude is extensive. (Dasgupta et al., 2008)

These conditions include GCA, cancer and infections, as well as RA, fibromyalgia, hypothyroidism and drug-induced myalgia. Furthermore, once a diagnosis has been made, existing clinical guidelines suggest an evaluation of whether patients have comorbidities that put them at greater risk of side effects from GC treatment. (Dejaco, Singh, Perel, et al., 2015) Therefore, to assess whether these guidelines are practical, it is necessary to understand what proportion of patients with PMR actually have any of these comorbidities, both at diagnosis and after.

A further complicating factor is that people aged over 50 years are most commonly affected by PMR. As aging is an important predictor of morbidity,

people in this age group frequently have more than one comorbidity. A recent study from Scotland found the proportion of adults with two or more chronic conditions increased from 30.4% between the ages of 45-64 years, to 64.9% and then greater than 80% in those aged 65-84 and over 85 years of age respectively. (Barnett et al., 2012) These findings have been replicated around the world, including in Italy where a recent observational study estimated that by the age of 65 approximately 40% of people have multiple morbidities. (Lenzi et al., 2016)

This systematic review aims to summarise the available evidence of the comorbidity profile of people with PMR. This will be the first review to assess comprehensively the evidence for all comorbidities and whether there is evidence for multiple comorbidities existing together. If the evidence shows that patients with PMR commonly have multiple comorbidities, then these may no longer be viewed as exclusion criteria precluding a diagnosis of PMR, potentially revealing the true burden of PMR to be higher than currently recognised.

5.2 Methods

This study was a systematic review and narrative synthesis of research literature. Medical bibliographic databases were searched to identify articles containing data on any comorbidity that have been described either prior to, or following, a diagnosis of PMR.

5.2.1 Data sources, searches and study selection

The search was conducted in MEDLINE, Embase, PsycINFO and CINAHL from their inception until the date of search in November 2016.

MEDLINE is a biomedical database which began in the 1960s and includes journal articles from 1946 onwards. It is run by the National Library of Medicine (NLM) in the United States. It holds citations from more than 5,200 journals from around the world but with a particular focus on North America. (US National Library of Medicine, 2018b) Alongside searches based around free text, it also has the additional functionality of the NLM controlled search vocabulary. These are named Medical Subject Headings (MeSH). MeSH terms are a hierarchically-organised terminology for cataloguing information, and articles are indexed by expert staff at NLM. (US National Library of Medicine, 2018a)

Embase is a database containing studies published in biomedical journals. It contains articles dating from 1947 and includes slightly more journals than MEDLINE, with a total of 8,500. However, while MEDLINE is free to use, Embase access incurs significant cost, but is available through the Keele Health Library.

Embase, similar to MEDLINE, has a hierarchically organised thesaurus based on biomedical indexing; within this database this system is called Emtree thesaurus. (Elsevier, 2017) Traditionally, Embase contained more European-centric research journal outputs, although many journals were indexed in both Medline and Embase. This meant the amount of coverage overlap between these two databases was previously estimated to lie between 34% (Smith et al., 1992) and, later, 70%. (Yonker et al., 1990) However, after 2010, Embase expanded significantly and now includes all MEDLINE titles. (Elsevier, 2017)

CINAHL (Cumulative Index to Nursing and Allied Heath Literature) is published by EBSCO and contains more than 2½ million records. This database lists citations from 1981 and predominantly focusses on nursing, allied health disciplines and biomedicine. Similar to Medline, the indexing thesaurus used in CINAHL utilises MeSH terms. PsycINFO is produced by the American Psychological Association and contains abstracts in the field of psychology. It extends to approximately 3½ million abstracts from 1967 to the present.

In order to ensure no studies were missed, all of these large databases were searched. The search strategy involved using ‘exploded’ “MeSH” or “thesaurus” terms “polymyalgia rheumatica” and “giant cell arteritis”. These were combined with the Boolean operator “or”. As these hierarchical index systems involve human input to index correctly, free text searches were also employed to find any study which included the free text “polymyalgia rheumatica”, “giant cell arteritis”, “PMR”, “GCA”, “Horton’s disease”, “Temporal arteritis”, “Cranial arteritis” or “senile arteritis”. In this way, the search strategy was as broad as possible to ensure all potentially relevant studies were included. Additional articles were

found by examining reference lists of included studies and an updated search was run in June 2018.

Giant cell arteritis, which is a vasculitis that very commonly co-occurs with PMR, was included in the search strategy due to the high proportion, approximately 10-30%, of patients with PMR who develop GCA at some point in the course of their disease. (Salvarani et al., 2002a; Weyand and Goronzy, 2003) It is clear that GCA is linked with PMR, but it was not to prove this association that studies referencing GCA were included. Rather, the reason GCA was used in the search was that, given the large overlap between conditions, it is likely that some studies which are referenced as covering GCA only may actually also include patients with co-existent PMR. Therefore, ensuring these studies were carried forward beyond the title screening stage minimised the chance of missing potentially relevant studies.

All the article titles identified were screened by a single reviewer (RP) against the inclusion and exclusion criteria. A random sample of 100 of these were reviewed by a second reviewer (TH) and agreement between decisions was assessed using adjusted Kappa calculation. (Byrt, Bishop and Carlin, 1993) Adjusted Kappa was used as a large number of studies were likely to be excluded, meaning this category would have a particularly high frequency compared to the included category. In order to determine adjusted Kappa, the observed agreement must first be determined, using the calculation detailed in table 5-1.

Table 5-1: Calculation of observed agreement

		Observer 1 (RP)		
		Included	Excluded	Total
Observer 2 (TH)	Included	a	b	g1
	Excluded	c	d	g2
	Total	f1	f2	n

$$P_{obs} = \frac{(a + d)}{n}$$

Once observed agreement has been determined, the adjusted Kappa is calculated as below, where *k* is the number of categories.

$$Adjusted\ Kappa\ = \frac{kP_{obs} - 1}{k - 1}$$

All selected abstracts were then assessed by two reviewers (RP & TH). Any citation thought to be eligible by either reviewer was carried forward to full text review. Reasons for exclusion were recorded. Finally, the remaining full texts were reviewed by the same two authors and a list of papers to be included in the narrative synthesis was created. PRISMA guidelines were followed throughout the review process. (Moher et al., 2009)

5.2.2 Inclusion and exclusion criteria

The inclusion criteria for this study were created around the aim of building a broad picture of the health of patients with PMR. The aims, as described earlier, were not to prove direct causation between PMR and specific conditions. Instead, the aim was to look for associations between PMR and a range of comorbidities, as well as the differences in the overall health status of patients with PMR compared to those without.

Therefore, wide inclusion criteria were employed to ensure that this review was a sensitive as possible in finding and evaluating any evidence of comorbidities in patients with PMR. For a study to be included in this review, it must have met all the following criteria.

1. Morbidity of interest: it must include patients with a diagnosis of PMR.
2. Outcome of interest: it must report at least one comorbidity.
3. Study design: must be either cross sectional, case-control or a prospective or retrospective cohort study.
4. There were no date or language restrictions

Including retrospective, contemporaneous and prospective studies allowed a full assessment of existing literature of any associations with comorbidities without a requirement that this association is causative.

Potentially relevant studies that contained data on GCA were included until full text review, due to the overlap between PMR and GCA. If, at that point, the paper only contained data about GCA without reference to PMR, they were excluded. The reference lists of other systematic reviews that had assessed individual

comorbidities related to PMR were also reviewed to ensure relevant studies not identified in the search were included.

If a study met any of the following exclusion criteria, they were removed from this analysis in order to ensure accuracy of findings.

1. Studies which reported results for patients under the age of 40 years
2. Randomised control trials (RCTs), review articles, conference abstracts
3. Studies that reported only complications of GC.

PMR is a disease of older adults. In order to make a diagnosis of PMR, clinical guidelines suggest patients must be aged over 50 years, (Dasgupta et al. 2012) therefore patients under 40 years old are likely to represent misdiagnosis or very atypical disease.

RCTs were excluded as their sample populations were less likely to be representative of all patients with PMR. The patients recruited into RCTs are often homogenous, that is to say they tend to employ restrictive selection criteria and exclude patients who have, for example, comorbidities that may affect the outcome of the trial. By making treatment groups very similar, investigators have the best chance of ascertaining with accuracy of whether a treatment is effective or not. However, by employing strict exclusion criteria, sampling bias is introduced and the populations that are examined within these studies become less like patients found in routine general practice. (Kennedy-Martin et al., 2015) Therefore, these studies do not reflect routine clinical practice and cannot provide data which is generalisable to all patients with a diagnosis of PMR.

Review articles and conference abstracts were not included to ensure all articles were peer reviewed and fully referenced. In order to ensure that all conditions represented true comorbidities of PMR, rather than secondary complications of GC treatment, trials in which the outcome measures were GC complications only, were excluded. (Chuang et al., 1982; Behn, Perera and Myles, 1983; Gabriel et al., 1997; Proven et al., 2003; Mazzantini et al., 2012; Albrecht et al., 2018; Paskins et al., 2018; Shbeeb et al., 2018a) Although, due to the fact GCs are near universally prescribed in the treatment of PMR, it was not possible to include only studies which included GC naïve patients only.

The reference section of all included papers were searched and any paper which was identified as meeting the previously detailed inclusion criteria were included. The screening process for these papers was the same as that employed for those identified during the initial database search.

5.2.3 Quality assessment

Both reviewers used the Newcastle-Ottawa scale, for case-control and/or cohort studies, (Wells et al., 2009) to evaluate the quality of studies. The Newcastle-Ottawa scale is an ongoing collaboration between the University of Newcastle, Australia, and Ottawa, Canada. Studies are judged on three outcomes: 1) selection and 2) compatibility of study groups as well as 3) ascertainment of either the exposure or outcome of interest. This scale was designed due to the difficulty of implementing and conducting non-randomised studies, such as case control and cohort trials. For example, because these types of studies are non-

randomised, it can be difficult to ensure similarity between treatment or exposure groups.

The scale is based on a star rating system and allows researchers to grade studies on their rigour. It relies on reviewers to assign a rating for each study in the three outcome areas. The checklist has received some criticism regarding low inter-rater reliability. (Hartling et al., 2013) However, it has been used in multiple published papers and importantly is endorsed for use in systematic reviews of non-randomised trials by the Cochrane collaboration. (Higgins and Green, 2011)

5.2.4 Data extraction

A standardised form was developed and used by both reviewers independently to ensure the uniformity and accuracy of data extraction (appendix 5). Information recorded from each study, including lead author name, publication year, sex, age, country and healthcare setting details were extracted. Further to this, other variables were also recorded, including population sizes, study design, chronology of data collection, (either prospective or retrospective), clinical criteria used in diagnosis of PMR, comorbidity(s) assessed, number and proportion of PMR or control patients affected by comorbidity, and the effect measures reported.

Comorbidities were categorised into four groups, namely (1) malignant diseases, including haematological malignancies; (2) vascular diseases, including

coronary, cerebro-arterial and peripheral arterial disease; (3) mortality and (4) other comorbidities (e.g. endocrine, psychiatric and neurological diseases).

5.2.5 Data analysis

Using the total number of patients with PMR and their controls, an attempt was made to aggregate data to obtain pooled estimates of prevalence of comorbidities and odds ratios to quantify the strength of any apparent association.

5.3 Results

5.3.1 Search results

A total of 27,698 articles were identified in the four databases searched with a further 6 identified following review of references of other articles and 1 more in the updated search in June 2018. Of this total, 10,376 were duplicates and therefore removed, leaving 17,329 unique articles. Following application of inclusion and exclusion criteria during screening of titles, 17,042 further citations were excluded.

Of the random selection of 100 of these articles, which were reviewed by a second author, the agreement between authors was assessed as below and found to be excellent (κ= 0.86).

Table 5-2: Agreement between reviewers at title review stage

		Observer 1 (RP)		
		Included	Excluded	Total
Observer 2 (TH)	Included	0	6	6
	Excluded	1	93	94
	Total	1	99	100

$$P_{obs} = \frac{(a+d)}{n}$$

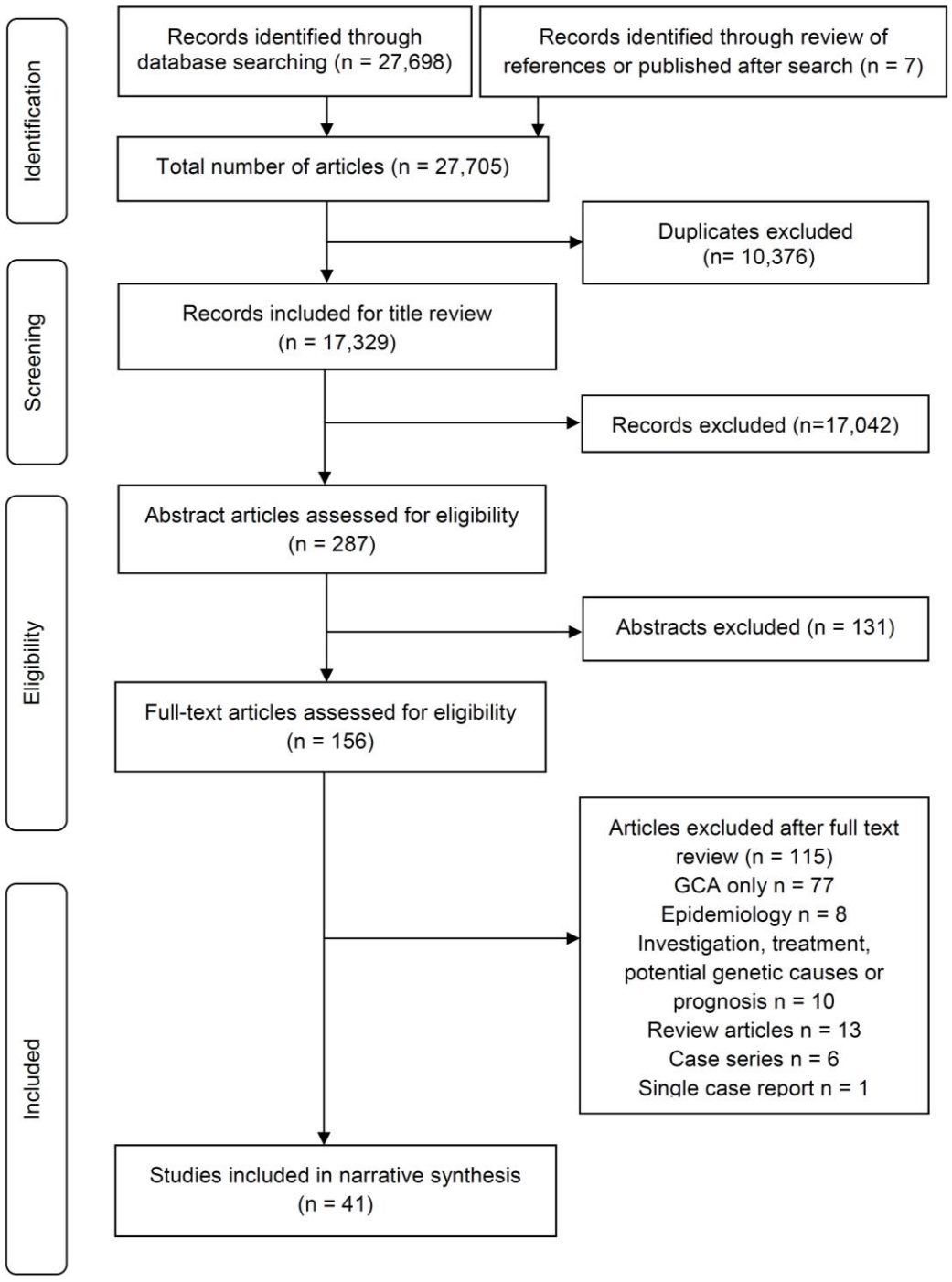
$$P_{obs} = \frac{(0+93)}{100} = 0.93$$

$$Adjusted\ Kappa\ = \frac{kP_{obs} - 1}{k-1}$$

$$Adjusted\ Kappa\ = \frac{(2 * 0.93) - 1}{2-1} = 0.86$$

At this stage, 287 papers remained for abstract review, which was undertaken by both reviewers. 131 studies were excluded at this time, leaving 156 for full text review. Following full text review, 41 studies were included for the analysis. The reasons for exclusion at full text review were: the subject of paper was GCA only, (n=77), review articles (n=13), articles describing investigation, treatment, genetics or prognosis (n=10) or others (n=15). This process followed PRISMA guidelines, (Moher et al., 2009) and is detailed in figure 5-1.

Figure 5-1: Flowchart of study inclusion, adopted from PRISMA guidelines (Moher et al., 2009)



5.3.2 Articles included in the review

Of the 41 included studies, 32 were cohort and 9 were case-control. 18 of the cohort studies did not use a formal comparator group. Of the 14 cohort studies with controls, six were based on national datasets, whereas 8 were either based on local datasets or patients presenting to clinics at the same hospital. PMR cases were defined from medical records in 16 studies, national registries in 19 and national databases in the remaining 6 studies. Co-existent GCA cases were formally excluded in 6 studies and included, or not explicitly excluded, in 35 studies. All but one study was from Europe (predominantly Scandinavia) or the United States.

5.3.3 Quality assessment

All the articles in this study used medical records or nationwide registries (based on medical records) to corroborate diagnosis of PMR and the chosen comorbidity. Therefore, they were awarded three or four stars for cohort or case selection using the Newcastle Ottawa criteria. All studies also achieved at least two stars for outcome measurement. However, many of the studies failed to recruit a comparator group, (n=19) instead using the population as a reference, therefore comparability scores were low for a number of the studies. The results, using the Newcastle-Ottawa scale, of quality assessment and the meta data (author, study location, year, study type, comorbidity and temporal relationship of comorbidity to PMR diagnosis) of each included study are summarised in table 5-3.

Table 5-3: Studies included in systematic review

Author	Study Location	Year	Study Type	Comorbidity(s) assessed	Temporal Relationship of Comorbidity	Quality Assessment		
						Selection	Comparability	Outcome
B. A. Bengtsson and Malmvall	Sweden	1981	Cohort	Vascular events	Prospective	4	0	2
Bowness et al.	United Kingdom	1991	Cohort	Thyroid disease	Prospective	4	0	2
Juchet et al.	France	1993	Cohort	Thyroid disease	Prospective	3	0	2
Haga et al.	Norway	1993	Cohort	Cancer	Prospective	4	1	2
Schaufelberger, Bengtsson, and Andersson	Sweden	1995	Cohort	Mortality	Prospective	4	0	2
J T Gran et al.	Norway	2001	Cohort	Mortality	Prospective	4	1	3
Doran et al.	United States	2002	Cohort	Mortality	Prospective	4	0	2
Uddhammar et al.	Sweden	2002	Cohort	Mortality	Prospective	3	0	3
Myklebust et al.	Norway	2002	Cohort	All cancer	Both	4	2	3
Myklebust et al.	Norway	2003	Cohort	Mortality	Prospective	4	1	3
Askling et al.	Sweden	2005	Case Control	Lymphoma	Retrospective	3	2	3
H. M. Kremers et al.	United States	2005	Cohort	Various	Prospective	4	2	3
Eaton et al.	Denmark	2007	Cohort	Autoimmune diseases	Cross-sectional	4	0	2
H. M. H. Kremers et al.	United States	2007	Cohort	Vascular events	Prospective	3	0	2
Warrington et al.	United States	2009	Cohort	Peripheral Vascular Disease	Prospective	4	2	2
Lesley A Anderson et al.	United States	2009	Case Control	Lymphomas	Retrospective	3	2	3
L A Anderson et al.	United States	2009	Case Control	Myeloid malignancies	Retrospective	3	2	3
Lesley A Anderson and Engels	United States	2010	Case Control	Leukaemia	Retrospective	3	2	3
Jianguang et al.	Sweden	2010	Cohort	Malignancy	Prospective	3	1	3
Kristinsson et al.	Sweden	2010	Case control	Myeloproliferative neoplasms	Retrospective	3	2	3

Author	Study Location	Year	Study Type	Comorbidity(s) assessed	Temporal Relationship of Comorbidity	Quality Assessment		
						Selection	Comparability	Outcome
Lanoy and Engels	United States	2010	Case Control	Skin Cancers	Retrospective	3	2	3
Eaton et al.	Denmark	2006	Cohort	Psychiatric	Retrospective	4	0	3
Kang, Sheu, and Lin	Taiwan	2011	Cohort	Stroke	Prospective	4	2	2
Lindqvist et al.	Sweden	2011	Case Control	Plasma cell cancers	Retrospective	3	2	3
Zoller et al.	Sweden	2012	Cohort	Stroke	Prospective	4	0	3
Zöller et al.	Sweden	2012	Cohort	Vascular events	Prospective	4	0	2
K. Hemminki, Liu, et al.	Sweden	2012	Cohort	Digestive tract cancer	Prospective	4	0	2
K. Hemminki, Liu, et al.	Sweden	2012	Cohort	Digestive tract cancer	Prospective	4	0	2
Kari Hemminki et al.	Sweden	2012	Cohort	Female cancers	Prospective	4	0	2
Kari Hemminki et al.	Sweden	2012	Cohort	Myeloma	Prospective	4	0	2
S. J. Chen et al.	Taiwan	2012	Case control	Schizophrenia	Retrospective	3	2	3
Li, Sundquist, and Sundquist	Sweden	2012	Cohort	Parkinson's disease	Prospective	4	0	2
Kari Hemminki, Li, et al.	Sweden	2012	Cohort	Obesity (hospitalisation)	Prospective	4	0	2
Muller et al.	United Kingdom	2013	Cohort	All cancer	Prospective	4	2	3
Hancock et al.	United Kingdom	2014	Cohort	Vascular events	Prospective	4	2	2
M. Fallah et al.	Sweden	2014	Cohort	Non Hodgkins Lymphoma	Prospective	4	0	2
Mahdi Fallah et al.	Sweden	2014	Cohort	Hodgkin lymphoma	Prospective	4	0	2
Pfefiffer et al.	United States	2015	Cohort	All cancers	Both	3	2	3
Pujades-Rodriguez et al.	United Kingdom	2016	Cohort	Vascular events	Prospective	4	2	2
Bellan et al.	Italy	2017	Cohort	Cancer	Prospective	3	0	3
Scrivo et al.	Italy	2018	Case control	Diverticular disease	Retrospective	3	2	3

5.3.4 PMR and cancer

Seven studies, reporting twelve outcome measures, have assessed the risk of cancer diagnosis prior to PMR onset, (table 5-4). All of the studies were case control in design and they assessed the risk of haematogenous cancers. Most studies assessed the risk of lymphoma or myeloproliferative diseases. Of the twelve outcome measures reported, the rate of haematogenous cancers was significantly higher among patients with PMR in five; while in the other seven, no significant differences were observed.

Table 5-4: Cancer prior to diagnosis with PMR

Retrospective case-control studies								
Author	**Diagnosis**	**Case**	**PMR**	**Control**	**PMR**	**Odds Ratio (95% CI)**	**Case Rate (%)**	**Control Rate (%)**
Anderson et al., (2009)	Lymphoid	33,721	344	122,531	1,244	0.9 (0.8-1.0)	1.02	1.02
Anderson et al. (2009)	Myeloid	9,998	125	160,086	1,288	1.7 (1.4-2.1)	1.25	0.80
	Myelodys-plastic	3,758	55	42,886	518	1.5 (1.1-2)	1.46	1.21
Anderson and Engels, (2010)	HCL*	418	9	160,086	2,721	1.5 (0.5-3.9)	2.15	1.70
Askling et al. (2005)	All lymphoma	42,676	114	78,487	250	0.8 (0.7-1.0)	0.27	0.32
	NHL*	28,355	88	52,164	187	0.9 (0.7-1.1)	0.31	0.36
	HL*	4,037	3	7,394	15	0.4 (0.1-1.3)	0.07	0.2
	CLL*	10,555	24	19,391	52	0.8 (0.5-1.4)	0.23	0.27
Kristinsson et al. (2010)	Any MPN*	11,039	46	43,550	104	1.7 (1.2-2.5)	0.42	0.24
Lanoy and Engels, (2010)	Cutaneous NHL*	2,652	19	178,452	1,731	0.7 (0.5-1.1)	0.72	0.97
Lindqvist et al. (2011)	MM	19,112	56	75,408	116	1.9 (1.4-2.6)	0.29	0.15
	MGUS*	5,403	58	21,209	79	2.9 (2.1-4.1)	1.07	0.37

* HCL (Hairy cell leukaemia), NHL (Non-Hodgkin lymphoma), HL (Hodgkin's lymphoma), CLL (Chronic Lymphocytic Leukaemia), MM (Multiple myeloma), MPN (myeloproliferative neoplasm), MGUS (Monclonal gammopathy of undetermined significance)

Six studies reported prospective rates of any cancer diagnosis after diagnosis with PMR (table 5-5); two showed an increase in the proportion of people with PMR who developed cancer compared to controls, two were equivocal and the remaining two found the opposite.

Table 5-5: Cancer following diagnosis with PMR

Prospective cohort- combined cancer cases						
	PMR cases	**Cancer cases**	**Proportion (%)**	**Controls**	**Cancer cases**	**Proportion (%)**
Muller et al. (2014)	2,877	667	23.18	9,942	1,938	19.49
Bellan et al. (2017)	100	24	24.00	702	41	5.84
Jianguang et al. (2010)	35,918	3,941	10.97			
Myklebust et al. (2002)	366	34	9.29	1,324	143	10.80
Haga et al. (1993)	91	10	10.99	794	131	16.50
Pfefiffer et al. (2015)	359	66	18.38	357	62	17.37
Total*	**39,711**	**4,742**	**21.12**	**13,119**	**2,315**	**17.65**
*Ji et al not included in calculation as no control group						

In six prospective cohort studies, the risk of 17 individual types of cancer following diagnosis with PMR was reported. Two studies showed an increase in the risk of Hodgkin's (Mahdi Fallah et al., 2014) and non-Hodgkin's lymphoma. (M. Fallah et al., 2014) Of the remaining four studies, three reported no difference in the rates of female cancers, (Kari Hemminki, Liu, Ji, et al., 2012) upper gastrointestinal cancers (K. Hemminki, Liu, Ji, et al., 2012a) or myeloma. (Kari Hemminki, Liu, Forsti, et al., 2012) The final study reported no difference in mortality following diagnosis with gastrointestinal cancers (K. Hemminki, Liu, Ji, et al., 2012b) among people with or without PMR.

5.3.5 PMR and vascular disease

A number of studies (n=8) assessed a variety of different vascular diseases in patients with PMR (table 5-6). In total, fifteen outcome measures were reported, however only seven gave comparable figures for patients without PMR. In each study with a comparator group the proportion of people with PMR who developed vascular disease was higher compared to controls.

Table 5-6: Vascular disease and PMR

Author	PMR cases	Comorbid condition	Proportion (%)	Controls	Comorbid condition	Proportion (%)
Stroke						
Kang, Sheu, and Lin (2011)	781	113	14.47	3,905	273	6.99
Zoller et al. (2012)	16,496	1,981	12.01			
H. M. H. Kremers et al. (2007)	276	58	21.01			
Hancock et al. (2014)	3,249	397	12.22	12,735	556	4.37
Myocardial infarction						
H. M. H. Kremers et al. (2007)	276	47	17.03			
Hancock et al. (2014)	3,249	460	14.16	12,735	575	4.52
Zoller et al. (2012)	21,351	5,669	26.55			
Heart failure						
H. M. H. Kremers et al. (2007)	276	68	24.64			
Peripheral vascular disease						
H. M. H. Kremers et al. (2007)	276	35	12.68			
Hancock et al. (2014)	3,249	140	4.31	12,735	151	1.19
(Warrington et al., 2009)	353	38	10.76	705	28	3.97
Combined						
H. M. H. Kremers et al. (2007)	276	208	75.36			
Hancock et al. (2014)	3,249	918	28.25	12,735	1,150	9.03
Pujades-Rodriguez et al. (2016)	9,776	2,272	23.24	105,504	21,559	20.43
B. A. Bengtsson and Malmvall (1981)	73	16	21.92			

5.3.6 PMR and mortality

Four studies assessed the association between PMR and mortality. Three reported reduced mortality among patients diagnosed with PMR (Gran et al., 2001; Doran et al., 2002; Myklebust et al., 2003) while one found an increase, however this study did not differentiate between patients with PMR and GCA. (Uddhammar et al., 2002)

5.3.7 PMR and other comorbidities

An association between thyroid disease and PMR is unproven. Bowness et al., (1991) found an increase in the risk of hypothyroid disease with a relative risk [RR] of 3.2 [95% confidence interval [CI] 1.71, 5.91] however, Juchet et al. (1993) did not. One recent case control study found a significantly increased rate of diverticular disease prior to a diagnosis with PMR with an odds ratio [OR] of 4.06 [95% CI 1.76, 9.35]. (Scrivo et al. 2018)

No evidence has been found to associate PMR with psychiatric comorbidities, including schizophrenia (Eaton et al., 2006; Chen et al., 2012) and bipolar disease, (Eaton et al., 2006) although Li et al (2012) found a potential association between PMR and Parkinson's disease [standardised incidence ratio [SIR] 1.25 [95% CI 1.01, 1.53] and an association between PMR and hospitalisation due to obesity SIR 1.65 [1.22, 2.19] has also been reported. (Kari Hemminki, Li, et al., 2012)

Two studies from the United States (Kremers et al., 2005; Pfefiffer et al., 2015) looked at wide ranges of different comorbidities, but the number of patients included in each study with PMR (n= 364 and n=193 respectively) were insufficient to find significant associations for the majority of the comorbidities.

5.3.8 Data analysis

Aggregation of data to calculate pooled odds and hazard ratios was attempted for vascular disease and cancer diagnoses; however, due to high levels of heterogeneity between the studies (88-100%), these results are not reported.

Despite this, five studies reported the absolute numbers of patients developing cancer, which meant that a calculation could be made of the proportion of patients with and without PMR who went on to develop a neoplasm. The proportion with PMR who developed cancer was 21.12% compared to 17.65% of patients without PMR.

Unfortunately, within the study periods reported, no more than two studies stated the absolute numbers of patients with and without PMR who developed stroke, myocardial infarction, heart failure, peripheral vascular disease or combined vascular disease outcomes respectively. Therefore, a proportion was not calculated for these morbidities.

5.4 Discussion

5.4.1 Statement of principal findings

This review found some evidence of an association between PMR and vascular disease and possibly cancer, particularly in the first six months following diagnosis. However, the evidence for this is not robust.

5.4.2 PMR and cancer

Retrospectively, prior to PMR diagnosis, five of the twelve outcomes reported by seven studies found an increased risk of cancer in patients who subsequently went on to develop PMR. All of these studies assessed haematogenous malignancies and also excluded PMR diagnoses made in the year prior to diagnosis of cancer, to reduce the risk of reverse causality- i.e. cancer causing PMR or PMR symptoms.

Prospectively, after PMR diagnosis, there appeared to be an increase in the risk of cancer diagnosis, however it was concentrated in the first six months following diagnosis. This could be due to a number of reasons, for example surveillance bias. Surveillance bias exists where an index medical condition leads to the discovery of another due to the diagnostic work-up or follow up necessary for management of the index condition. (Haut and Pronovost, 2011) A recent study from Scandinavia, authored by the same group that has produced many of the studies into comorbidities in PMR, illustrated this by demonstrating that rates of urological cancer were much higher following diagnosis with renal calculi. This

increase in the rate of cancers was concentrated in the first year following diagnosis, although some increase in risk persisted even after ten years of follow up. (Hemminki et al., 2017)

A second potential reason for the apparent link between PMR and cancer, in the first six months following diagnosis, could be an element of misdiagnosis. Many of the features of PMR, such as myalgia, fatigue, weight loss, and raised inflammatory markers are also non-specific early features of some cancers. These explanations are supported by the fact that, as time passed, the rate of diagnosis of cancer dropped down to the background population rate. Furthermore, the treatment of PMR, a moderate dose of GC, will also in many cases lead to a temporary improvement in these constitutional symptoms.

Regarding specific types of cancer following PMR diagnosis, a number of studies have looked into the associations between PMR and haematological cancers. Positive findings have been tentatively suggested for both Hodgkin's and non-Hodgkin's lymphoma, (M. Fallah et al., 2014) Again, it may be the case that these results are again due to surveillance bias or incorrect diagnosis. However, an increase in the risk of lymphoma has been observed with RA. The reason for this has been postulated to be that the higher accumulated inflammatory activity in RA may lead to dysfunction within the immune systems of patients. (Hellgren et al., 2017) As PMR is also characterised by raised inflammatory levels, it could be that a similar mechanism may lie behind the apparent increase in rates of certain haematogenous malignancies in patients with PMR.

5.4.3 PMR and vascular disease

The overall trend of results suggests PMR may be associated with an increased risk of the development of vascular disease. However, the two largest studies, which were both based on population data from the UK, reported conflicting results, Hancock et al (2014) stated that PMR was significantly associated with vascular disease, while Pujades-Rodriguez et al (2016) reported a reduction in the risk incidence rate ratio [IRR] of 0.88 [95% CI 0.83, 0.94]). Although, in the latter study and when only patients with PMR were included, there was a slight increase in the proportion of patients with PMR who went on to have a vascular event compared to controls (23.24% compared to 20.43%).

These two studies employed similar approaches in selecting patients with PMR from UK databases. However, a number of small methodological differences existed between the studies. Hancock et al (2014) restricted the age of participants to only those aged >50 years while, in the study from Pujades-Rodriguez et al (2016), the age restriction was patients aged >18 years. The difference in age distribution in each study may account for part the contrasting findings. Other differences were seen in the average number of years of follow up, at 7.8 and 3.13 respectively, as well as the total number of patients found with PMR: 3,249 compared to 11,320. As the follow up period was longer, it may be that the increased overall risk found by Hancock et al (2014) was concentrated further away from date of PMR diagnosis. However, as discussed previously, although the headline findings from Pujades-Rodriguez et al. (2016) were that no increase in the vascular risk was found, the rate of vascular events were still slightly higher than controls when PMR patients alone were considered.

Another potential reason for the inconsistency in evidence of the effect that PMR has upon vascular risk may be the modulating effect that GCs have upon levels on inflammation in the blood vessels of patients with PMR. As discussed earlier, the increased risk of vascular disease among patients with RA has been postulated to be due to higher levels of arterial atherosclerotic plaques, (Jonsson et al., 2001; Pamuk, Ünlü and Çakir, 2006) the quantity of which correlates with levels of inflammation (Kumeda et al., 2002) and duration of rheumatological disease. (Dessein et al., 2007)

If the excess risk of vascular disease is strongly associated with the presence of inflammation in the body, then the administration of anti-inflammatory therapy, such as GCs, may reduce the excess vascular risk by lowering the levels of systemic inflammation. The study published by H. Kremers et al. (2007) appears to confirm this. In this study, the risk of vascular events was lower in patients with PMR who were treated with GCs compared to those who were not. Further to this, it was noted by Hancock et al. (2014) that the excess vascular risk in PMR reduced over time; this could reflect declining levels of inflammation. This is in contrast to the lifelong increased inflammation associated with other rheumatological conditions, such as rheumatoid arthritis.

However, to add a further layer of complexity, it is known that GC therapy alone increases a person's risk of developing complications such as hypertension and obesity, (Moghadam-Kia and Werth, 2010) which are risk factors for vascular disease. Therefore, it may be that the reduction in vascular risk toward baseline levels observed in the months after diagnosis reflect either reduction in inflammation levels in the body due to successful treatment with GCs or a

reduction in the proportion of patients receiving GC therapy, or dose tapering in those who remain on treatment.

Overall, although the evidence is not currently unanimous, it appears that a diagnosis of PMR increases an individual's risk of vascular disease. However, further research in this area is needed to add clarity.

5.4.4 PMR and mortality

Conversely, the studies that reported the risk of mortality in patients with PMR found that the risk of death appears to reduce in the years following diagnosis with PMR. This was demonstrated in three out of the four studies that reported it as an independent outcome. A possible explanation for this could again be surveillance bias. Patients with chronic illness (and especially for PMR where regular assessment, follow up and monitoring are advised) are more likely to be under active follow up for their condition and any developing morbidity, particularly if related to well recognised adverse effects of treatment, is likely to be identified and managed earlier.

5.4.5 PMR and other morbidities

Two studies found evidence that patients with PMR may be more likely to develop hypothyroidism, an immune mediated endocrine disease, (Bowness et al., 1991) and Parkinson's disease, a neurological condition, (Li, Sundquist and Sundquist, 2012) respectively. PMR and hypothyroidism both preferentially affect females,

therefore a similar autoimmune pathway may be present in both conditions. However, as has been pointed out, PMR does not share all the characteristics of traditional autoimmune conditions, for example it lacks specific autoantibodies. (Floris et al., 2018)

Parkinson's disease is a condition which predominantly affects older people, as does PMR, therefore this association may be a result of clustering of diagnoses in an older population.

5.4.6 Strengths and weaknesses

The main strength of the study was its deliberately broad scope, and stated aim to include any study in which the risk of any comorbidity, either before or after diagnosis with PMR. A large number of duplicate studies were identified, which given the cross over between Embase and Medline databases, was to be expected. However, using both databases, although costly in terms of time through duplication of work and resources, ensured that every effort was made to include all studies which may be potentially relevant. Another strength was the exclusion of 'grey literature' after the initial broad search. This meant that only articles fully published in peer reviewed journals were included in the review, increasing the quality of the reviewed literature.

The potential limitations in this study arose not due to the protocol but rather as, despite the requirement for them to be peer reviewed, the majority of studies were relatively poor quality. The main biases identified included selection bias, surveillance bias and a lack of adequate control groups.

Selection bias was a problem in the design of many of the studies in this review, as PMR cases were often drawn from secondary care, either from hospital discharge data or rheumatology outpatient clinics, (n=19) . Current UK guidelines suggest only referring patients who present atypically, or in the case of diagnostic or treatment uncertainty, (Dasgupta et al., 2010; Dejaco, Singh, Perel, et al., 2015) meaning that, as previously discussed in the UK, 71-84% of patients with PMR are treated in the community by primary care physicians. (Barraclough et al., 2008; Yates et al., 2016) Therefore, the patient population in these studies may not accurately reflect the majority of those who are diagnosed with PMR. This may artificially inflate the apparent differences in development of comorbidities between patients with and without PMR.

Another limitation is the risk of surveillance bias, as discussed earlier around the apparent changes in risk around cancer, vascular disease and overall mortality. Some of the case-control studies attempted to deal with this by excluding comorbid disease found in the year prior to diagnosis, (L A Anderson et al., 2009; Lesley A Anderson et al., 2009; Anderson and Engels, 2010; Lindqvist et al., 2011). While Hancock et al. (2014) and Pujades-Rodriguez et al. (2016), in the two largest prospective observational cohort studies of vascular risk, selected controls that had contacted a primary care service in the year the index cases were diagnosed, in order to attempt to control for surveillance bias.

Another weakness of a number of these studies, was that they assessed multiple variables, often >30 different autoimmune conditions. These studies were predominantly from Scandinavia, registry based and looked into links between autoimmune conditions and specific cancer types. Due to the large number of

potential outcomes assessed, the risk of reporting a finding which was due to chance, a type I error, was much greater.

Another important variable to address is the potential influence on the risk of comorbidities of GC therapy in PMR. As GCs are the only widely accepted treatment for PMR, it is not possible to include only studies where patients were not treated with GCs as, for ethical reasons, they did not exist. However, as previously discussed, studies that exclusively reported the risk of comorbidities directly related to GC therapy were excluded. Further to this, in patients with a diagnosis of PMR, the duration and total dose of GC therapy varies widely and GCs are used to treat a broad range of conditions in addition to PMR. Therefore, GC therapy could act as a confounder in these studies which is difficult to control for.

A further drawback of the studies in this review was related to the fact that many of the cohort studies identified failed to include comparison groups (n=18). In these cases, indirect standardisation was used to calculate incidence or mortality ratios. The lack of matched comparison groups limits the accuracy and generalisability of many of the studies and meant they scored poorly using the Newcastle-Ottawa scale of quality assessment. However, as this study aimed to build up a picture of the overall health of patients with PMR, rather than prove causation, these studies were still regarded as useful.

Furthermore, the range of comorbidities reported in the literature was more limited than expected, for example, there were no studies which explicitly examined the risks of important and common conditions such as diabetes mellitus and asthma or other chronic obstructive pulmonary disease. This

restricted range of comorbidities was due to the fact that many of the studies limited themselves to assessing a small number of comorbid conditions. Almost all the existing literature examined the link between PMR and cancer or vascular disease, to the neglect of other common conditions. The two studies which did attempt to look at a range of comorbidities were unfortunately underpowered. (Schaufelberger, Bengtsson and Andersson, 1995; Kremers et al., 2005) This means that the overall picture of the health of patients with PMR is not clear.

5.4.7 Conclusion

This review has found the overall standard of evidence regarding the prevalence of comorbidities in patients with PMR to be weak. There may be an increased risk of vascular disease, and possibly cancer in patients with PMR. Weaker quality evidence suggests, however, that patients with PMR have a reduced mortality rate. Currently, there is little evidence around the wider health of patients with PMR either at the time of, or after, diagnosis.

This lack of firm evidence of what comorbidities exist alongside, or are potentially associated with, PMR presents a problem for the pragmatic clinician, both in primary and secondary care. Current guidance suggest that during the diagnosis of PMR clinicians should exclude mimicking conditions, such as non-inflammatory, inflammatory (such as giant cell arteritis or rheumatoid arthritis), drug-induced, endocrine, infective and neoplastic conditions. (Dejaco, Singh, Perel, et al., 2015) However, comorbidities are very common in the age group affected by PMR, (Piccirillo et al., 2008) and this review shows there is some

evidence that patients with PMR are at least as likely to be diagnosed with some of these conditions compared to the general population. This means in clinical practice, the coexistence of one of these comorbidities with PMR is almost inevitable and should not necessarily prevent or invalidate the diagnosis of PMR. This knowledge may allow re-evaluation of guidelines and may, in turn, lead to an increase in the estimates of incidence and prevalence of PMR.

Further research is also required to ascertain the rate of diagnosis of comorbidities in patients with PMR and to confirm whether, and if so to what extent, a diagnosis of PMR imparts an excess risk of vascular disease or cancer. The following chapter describes large observational studies, based in primary care, of the prevalence of comorbidities before and after diagnosis in patients with PMR compared to matched controls.

Chapter 6 COMORBIDITIES IN POLYMYALGIA RHEUMATICA: EPIDEMIOLOGICAL CASE CONTROL AND COHORT STUDIES

This chapter contains a retrospective observational case control study and a prospective observational cohort study of comorbidities in people with PMR using the Clinical Practice Research Datalink (CPRD).

6.1 Introduction

The mean age of onset of PMR is around 73 years. (Doran et al., 2002) As discussed in chapter 5.1, as people age, they are much more likely to develop multiple chronic diseases, this effect is particularly pronounced in patients who are over 70 years of age. (Barnett et al., 2012) Therefore, many patients with PMR are demographically likely to have one or more chronic diseases.

The systematic review of existing literature described in the previous chapter found the overall standard of evidence of the rate of comorbidities in PMR was weak, and that there was no evidence at all for many conditions, such as asthma, COPD and diabetes. It is therefore uncertain whether a diagnosis with PMR affects the risk of being diagnosed with other comorbidities.

The existing evidence is, therefore, limited both by the relatively narrow range of comorbidities assessed and the standard of evidence available. This chapter, which describes a large scale epidemiological study of a broad range of comorbidities in patients with PMR, aims to address both of these shortcomings. The broad range of comorbidities will increase the number of comorbid conditions assessed beyond what has previously been reported in PMR, while the large

scale of the study will ensure the study has sufficient power to derive meaningful conclusions.

6.1.1 PMR and comorbidities

In this study a comorbidity is defined as “any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease [PMR] under study”. (Feinstein, 1970) It is important to establish which comorbidities coexist with PMR for a number of reasons. For example, as previously discussed, joint guidance produced by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) suggests that in order to make a PMR diagnosis, relevant mimicking conditions be excluded. (Dejaco, Singh, Perel, et al., 2015)

These mimicking conditions are extensive and include, but are not limited to, other inflammatory diseases, for example giant cell arteritis (GCA) or rheumatoid arthritis (RA), non-inflammatory conditions (osteoarthritis), drug-induced symptoms (for example, side effects of statin medications) , endocrine (thyroid disorders), infections (influenza) and neoplastic diseases. Some symptoms (myalgia, fever, tiredness, weakness) and laboratory findings (elevated inflammatory markers) that appear around the onset of many of these conditions are similar to the hallmarks of PMR. The importance of ensuring that patients are not misdiagnosed with PMR instead of potentially life threatening conditions, such as cancer, is understandable.

However, different rheumatological diseases having similar presenting features is not unusual and does not necessarily preclude diagnosis with both conditions. For example, rheumatoid arthritis (RA) and fibromyalgia both cause patients increased pain, fatigue and disability. However, unlike in the guidelines for PMR, RA is not regarded as an exclusion in the diagnosis of fibromyalgia, indeed it is increasingly recognised that patients with RA are at high risk of subsequently developing fibromyalgia. (Gist et al., 2018)

The guidelines for PMR are clinical classification, rather than diagnostic, criteria. These criteria were designed to produce homogenous groups of patients for research purposes, with a certainty of diagnosis greater than that required for routine clinical practice. However, in the absence of confirmed diagnostic criteria, it has been reported that clinical classification criteria are commonly used in clinical practice, particularly in rheumatological diseases. (June and Aggarwal, 2014)

Underpinning these guidelines was a study in which the sensitivity and specificity of a range of clinical and laboratory features of PMR were compared in patients with PMR to those with one of a number of other conditions, such as RA, connective tissue diseases, shoulder conditions, fibromyalgia and generalised osteoarthritis. (Dasgupta et al. 2012) The clinical features investigated in the study included duration of symptoms, neck or bilateral shoulder or hip girdle ache, weight loss, morning stiffness, shoulder or hip pain and tenderness as well as carpal tunnel syndrome and peripheral synovitis or other joint pain. The results of laboratory investigations such as CRP (C-reactive protein), ESR (Erythrocyte sedimentation rate), RF (Rheumatoid factor) and/or ACPA (anti–citrullinated protein antibody) were also assessed.

This study was unable to demonstrate any single symptom, sign or investigation that could differentiate between patients with a diagnosis of PMR when compared to those with other connective tissue diseases such as RA. Therefore, the study's authors advised an approach to PMR diagnosis in which confirmation of the presence of certain symptoms and investigation findings, such as bilateral shoulder pain and elevated ESR or CRP, and that absence of others, particularly peripheral synovitis and positive RA serology, were necessary for diagnosis. A patient with this constellation of symptoms and investigation findings could then be regarded as likely to have PMR, although only in the absence of an alternative diagnosis.

This tentativeness around diagnosis may have unintended consequences. Potentially patients may have a mimicking condition in addition to PMR, however, in this situation the guidelines would advise against a diagnosis of PMR being made. This could mean that current estimates of the incidence and prevalence of PMR underestimate the total burden of disease and mean that patients with a mimicking comorbidity may not be treated appropriately for their PMR. This effect may be exacerbated by the difficulty in recognising the difference between pathological increases in aching and pain compared to the well-established increases in frailty, aches, pains and even inflammatory markers that occur as people age. (Buckinx et al., 2015) Therefore, estimating the prevalence or likelihood of comorbidities in patients with PMR is important.

6.1.2 Reasons why comorbidities may be associated with PMR

Further to this, as discussed in chapter five, uncertainty surrounds whether a diagnosis of PMR actually predisposes people to an increased likelihood of development of other important comorbidities. There are a number of potential pathways through which this situation may arise. For example, a theoretical comorbidity may be associated with PMR due to similar autoimmune inflammatory processes. (Eaton et al., 2010) Other reasons for an increased risk of a comorbidity in PMR could be due to the increased levels of inflammation that occur in PMR, or the treatment of PMR with GCs, or simply as a patient ages. Each of these will be considered in turn.

6.1.3 Autoimmune association

It is well established that several autoimmune conditions co-exist in patients and cluster within families, although the exact pathophysiological mechanism is not known. (Somers et al., 2006) Examples of these clusters include thyroid disease and pernicious anaemia, vitiligo and multiple sclerosis; type one diabetes and primary biliary cirrhosis, and rheumatoid arthritis with Sjogren's syndrome. (Cárdenas-Roldán, Rojas-Villarraga and Anaya, 2013) PMR shares many characteristics with these conditions, such as raised inflammatory levels, improvement in symptoms following administration of GC therapy and an increased risk of diagnosis in women. Therefore, given PMR may share an autoimmune inflammatory process with other similar conditions, it may lie within a cluster of these diseases.

6.1.4 Links to raised inflammatory markers

Current published evidence suggests that patients with PMR may have an increased risk of vascular disease. (Hancock et al., 2014) However, the overall level of evidence for many conditions was weak and no comprehensive investigation has been undertaken into all potential comorbidities. (Partington et al., 2018) This potential association with vascular disease could be similar to the relationship that has been proven between vascular disease and gout, (Clarson et al., 2013) as well as with rheumatoid arthritis (RA), (Avina-Zubieta et al., 2012) and systemic lupus erythematosus. (Maureen McMahon, Bevra H Hahn, 2013). Each of these three conditions are inflammatory in nature and are associated with an increased risk of vascular disease, in fact the latter two conditions are now included as part of the latest version of the QRISK3® calculator that is widely used in clinical practice. This calculator provides information to healthcare professionals to personalise primary prevention of cardiovascular disease by estimating the ten-year risk of a heart attack or stroke based on individual patient factors. (Hippisley-Cox, Coupland and Brindle, 2017) Given the pathophysiological similarity between these conditions, there is biological plausibility that PMR and vascular disease could also be associated.

Some evidence for the association between levels of inflammation in PMR and development of vascular disease, as well as the reason for inconsistent study findings, was suggested in a small US study by Kremers. In this study it was shown that the risk of vascular events was lower in patients with PMR who were treated with GCs were compared to those who were not. (H. M. H. Kremers et al. 2007) This would add weight to the hypothesis that the inflammatory burden in

PMR is the driver for an increased risk of vascular disease; as GCs would reduce this burden of inflammation. Further to this, it was noted by Hancock that the observed excess vascular risk in PMR that reduced over time following diagnosis; this could reflect the progressive reduction in the level of inflammation in the body after diagnosis. (Hancock et al., 2014)

6.1.5 Glucocorticoid complications

The recommended, and only proven, treatment for PMR is glucocorticoids, of which the usual first choice agent in the UK is prednisolone. This class of medication is associated with significant and numerous adverse effects including increasing the risk of diabetes and hypertension, (Mazzantini et al., 2012) among other cited complications such as impaired immune response, cataracts, glaucoma and fragility fractures. (Moghadam-Kia and Werth, 2010) As such, GC related side effects need to be considered as potential co-morbidities that may present following diagnosis with, and treatment of, PMR. Furthermore, the use of prolonged GC therapy has also in itself been associated with an increased risk of cardiovascular disease. (Fardet, Petersen and Nazareth, 2012). As a result of this, the use of regular GC medication is also part of the QRISK3® calculator. (Hippisley-Cox, Coupland and Brindle, 2017)

However, the differential contribution of GCs in the development of comorbidities may be difficult to estimate as they may, through different mechanisms, act to increase or decrease the risk of a comorbidity. For example, as long term GC treatment increases the risk of obesity, as well as diabetes and hypertension, then it will inevitably increase the risk of vascular disease. However, at the same

time, GCs will also reduce levels of inflammation in the body in patients with PMR, which may lower the risk of vascular disease. It may be that in patients with PMR, the overall the risk of vascular and other conditions remains the same when compared to matched controls due to this effect.

6.1.6 Increasing morbidity due to age

The rate of multimorbidity climbs steeply after the age of 50, from 30.4% between the ages of 45-64 years, to 64.9% and greater than 80% in those aged 65-84 and over 85 years of age respectively. (Barnett et al., 2012) As PMR predominantly affects older people it is very likely a significant proportion of them will also have other chronic health conditions.

6.1.7 Study aims

This uncertainty inherent in the natural history, diagnosis and potential illness course of PMR is communicated implicitly to patients. One recent study investigated the level of information given to patients with a new diagnosis of PMR and found that almost 40% of patients did not receive written information at the time of their diagnosis. (Tshimologo et al., 2018) Another survey of members of PMRGCAuk (a UK based charity which supports people with PMR or GCA) found that patients wanted to receive more information around reducing glucocorticoids and the risks and benefits of treatment. (Muller et al., 2018)

Therefore, it is of upmost importance to firmly establish the health of patients at the time of, and subsequent to, diagnosis of PMR. This will inform both clinical classification criteria and diagnostic pathways. Furthermore, this will sharpen primary care's ability to monitor for signs of any comorbidities associated with PMR, and, where appropriate, to refer patients promptly to specialist care.

The study hypothesis is that patients with PMR may have a greater number of comorbidities at the time of diagnosis when compared to similar patients who do not have PMR and, given the evidence discussed above, a predisposition to develop certain comorbidities, particularly vascular disease, neoplasia and autoimmune conditions.

6.2 Methods

6.2.1 Data source

This investigation included both retrospective case control, and prospective cohort, studies carried out using the Clinical Practice Research Datalink (CPRD), which was described in detail in chapter 2. To briefly recapitulate, data in CPRD is collected in the course of routine primary care consultations. Of people who live in the UK 98% are registered with a General Practitioner, (Office for National Statistics, 2012a) and around 90% of patient contacts in the UK with the NHS is via primary care. (Hippisley-Cox and Vinogradova, 2009)

CPRD contains data collected on more than 17 million contributing patients within 718 (7.5% of the total) UK general practices and is representative of the UK population in terms of age, sex and ethnicity. (Herrett, Gallagher, et al., 2015) In this study, the presence or absence of PMR and any comorbidity will be based on physician diagnoses recorded as Read codes. This follows the methodology used in previous CPRD studies of comorbidities. (Kuo et al., 2016; Rees et al., 2017)

6.2.2 Study population

In this study, the exposed group were patients with a diagnosis of PMR recorded in their electronic healthcare records (EHR). They were identified in the study described in chapter 3. Each patient had a Read code diagnosis of PMR and two prescriptions of GCs, the first made within six months of PMR diagnosis, and the

second within six months of the first. No diagnoses of PMR made when patients were under the age of 40 years were accepted. This methodology replicates previous studies performed in CPRD of PMR. (Smeeth, Cook and Hall, 2006; Hancock et al., 2014; Muller et al., 2014; Paskins et al., 2018) In addition to these requirements, each patient must have at least three years of continuous follow up prior to date of diagnosis with PMR. The date of diagnosis with PMR is hereafter known as 'the index date'.

6.2.3 Matching

Each case was matched with up to five and no fewer than three controls. The number of controls per case was set at this level for pragmatic reasons. The increased statistical power generated by matching ever more controls per case diminishes rapidly above five controls per case, (Clayton and Hills 2013) therefore this was an acceptable upper limit. Cases with fewer than five but greater than two matched controls were also included. This meant that the overall number of cases included could be maximised and specifically those cases where there a smaller pool of possible controls, for example the very elderly, were included in the study.

The matching criteria employed were: 1) year of birth +/- 3 years, 2) sex and 3) registered in the same general practice. A further requirement was that in order for a control to be matched to a case, they must have been contributing data on the index date of their matched case. This index date of the case was then

assigned to each matched control. Exactly the same as with the cases, all of the controls must have at least 3 years of follow up prior to the index date.

6.2.4 Study period

Data recorded between 1st January 1990 and 1st January 2016 was analysed. The study start and end dates differed for the case control and cohort studies.

For the case control study, patients were included after the latest of four events: 1) the study start date, 2) the date at which they became 40 years old, 3) the date they registered at a participating practice plus six months, or 4) the date at which the practice was adjudged to reach internal quality standards; known as the 'up-to-standard date'. As in the previous studies, (chapters 3 and 4) an additional six months was added to the most recent registration date with a practice in order to ensure prevalent diagnoses were not included in the analysis. Data collection ended one year prior to index date. This was to minimise the chance of surveillance bias - PMR may be more likely to be diagnosed after diagnostic investigations that occur as a result of the comorbid condition. This strategy has been employed in other case control studies of comorbidities found in patients with PMR and gout. (L A Anderson et al., 2009; Kuo et al., 2016)

In the cohort study, the start of the study period was defined as the index date for each participant. Data collection ended at the earliest of five events: 1) the end of the study period, 2) the date when a patient transferred out of a practice, 3) the date of death, 4) the last date of data collection from the practice, or 5) the date of diagnosis with a comorbidity.

6.2.5 Comorbidity prevalence

Case Control

For the case control study, the Charlson index score and prevalence of the stratified and composite comorbidities were calculated at three time points prior to index date. The time points were at five, two and one year prior to index date. Prevalence was calculated by dividing the total number of people with the comorbidity (numerator) by the denominator, which was either the number of patients with PMR or their controls. The denominator figure was the same at one and two years prior to diagnosis but slightly less at five years. This was because, in order for a patient to be included in this study they must have contributed data for at least three years prior to index date. Therefore, although all of the patients included in this study contributed data at one and two years prior to index date, not all had five or more years of data.

Cohort

The follow up period for the cohort study was ten years. There was no minimum requirement for follow up following index date. Therefore, some patients were able to leave the study before they had developed a comorbidity whilst others contributed 10 years of data. Each outcome was separately assessed and patients were defined as at risk if they had not developed the outcome of interest. Person time was censored at a number of time points:

1) Ten years following index date
2) Transfer away from a practice contributing to CPRD

3) Death due to any cause
4) The final date that data was collected from this practice by CPRD

The censored patients contributed data until the date at which they left the study. Therefore, at any specified time-point following index date, a patient could be classified as being in one of three states, either:

1) Having developed the event of interest
2) Being at risk of the event of interest
3) Having previously been lost to follow up (censored)

When calculating the cumulative prevalence of each comorbidity, or the Charlson comorbidity index value, all diagnoses made prior to index date were included in order to better estimate health status at each time point following index date.

6.2.6 Covariates

Alcohol consumption

Alcohol consumption is recorded within CPRD as units of alcohol consumed per week. The formula for determining units of alcohol per drink is:

$$Volume\ of\ drink\ (ml) * \frac{Alcohol\ by\ volume\ (\%)}{1{,}000\ (ml)} = Alcohol\ units$$

A pint (568ml) of moderate strength (4%) beer will therefore contain 2.3 units of alcohol. Recent UK government guidelines have reduced the recommended maximum weekly intake of alcohol to 14 units for both men and women. ("UK Chief Medical Officers' Low Risk Drinking Guidelines", 2016) As levels of alcohol

consumption vary during a person's life then data recorded in CPRD will also. Therefore, for this study the most recent occasion this information was recorded prior to index date was used, which follows the methodology of other CPRD studies. (Paskins et al., 2018)

Furthermore, following the methods of Paskins et al. (2018) and C.-F. Kuo et al. (2016), the alcohol consumption data was converted into four categories. These categories were, 1) those who had never consumed alcohol or did not at that time, 2) those who consumed less than 10 units of alcohol per week, 3) those who consumed 10 or more units of alcohol per week and, finally, 4) those where the data was missing.

Smoking status

Similarly, the smoking status, if recorded by the primary care electronic health record, is included in CPRD. Again, the last time status was recorded prior to index date was used. Three categories were created, 1) those who had never smoked or were currently ex-smokers, 2) current smokers and 3) those in which the data was missing. Again, this follows the methods used by Paskins et al. (2018) and C.-F. Kuo et al (2016).

Body mass index data

Body mass index (BMI) is calculated using the equation:

$$BMI = \frac{weight\ (kg)}{height(m)^2}$$

Following previous CPRD studies, five categories were created for this data 1) “underweight” (BMI <18.5), 2) “normal” (BMI 18.5-24.9), 3) "overweight” (BMI 25-29.9), 4) "obese” (BMI>=30) or 5) "missing”. The categories created in this study follow convention in the interpretation of BMI. (‘Health Survey for England 2015: Adult overweight and obesity’, 2015)

6.2.7 Comorbidities

The selection of comorbidities utilised a three-step process.

Stage one

The initial starting point for selection of comorbidities was the Charlson comorbidity index. (Charlson et al., 1994) This index contains 17 diagnostic categories across a range of health domains that are each assigned a value according to their severity. By adding the scores together for each patient an overview of an individual’s health status can be obtained. This index has previously been mapped from the International statistical classification of diseases and related health problems (ICD) 9 classification to Read codes and has been used in previous studies of comorbidities in the CPRD dataset. (Kuo et al., 2016) The index has also been used in a study of comorbidities in patients

with PMR, albeit the study in question was of a small prospectively recruited cohort in the United States. (Kremers et al., 2005)

The Charlson index contains the following comorbidities (table 6-1):

Table 6-1: Charlson comorbidity index

Broad disease groups	Condition	Points
Vascular	Myocardial infarction	1
	Congestive heart failure	1
	Peripheral vascular disease	1
	Cerebrovascular accident	1
Neurological	Hemiplegia, paraplegia	2 *
	Dementia	1
Respiratory	Chronic pulmonary disease	1
Autoimmune, Rheumatological and Musculoskeletal	Any connective tissue disease	1
Gastroenterology	Peptic ulcer disease	1
	Mild Liver disease	2
	Moderate or severe liver disease	3
Endocrine	Diabetes	1
	Diabetes with chronic complications	2 **
Renal	Renal disease	2
Neoplastic	Solid tumour, leukaemia, lymphoma	2
	Metastatic solid tumours	6 +
Infectious Diseases	Acquired immunodeficiency syndrome	6

* If hemiplegia do not count CVA separately
** Do not count DM separately
+ If metastatic do not count cancer separately

Patients with higher scores calculated using the Charlson index, have higher mortality rates over a ten year period. (Charlson et al., 1994) The score has been validated in other conditions, including in patients with acute coronary syndrome (Radovanovic et al., 2014) and those discharged from hospitals in six countries. (Quan et al., 2011) Although the Charlson index was based on secondary care

data, it has also been used in primary care to define comorbidities. (Crooks, West and Card, 2015)

As previously discussed, only one study has previously assessed the prevalence of comorbidities in patients with PMR using all of the Charlson index. (Kremers et al., 2005) However, the systematic review in chapter 5 showed that a number of studies have considered the association between PMR and individual or small groups of comorbidities from within it. These include between PMR and vascular diseases, (B A Bengtsson and Malmvall, 1981; Warrington et al., 2009; Kang, Sheu and Lin, 2011; Zoller et al., 2012; Hancock et al., 2014; Pujades-Rodriguez et al., 2016) neurological, (Li, Sundquist and Sundquist, 2012) rheumatological, (Eaton et al., 2007) endocrine, (Bowness et al., 1991; Juchet et al., 1993; Eaton et al., 2007) and neoplastic conditions. (Haga et al., 1993; L A Anderson et al., 2009; Anderson and Engels, 2010; Lanoy, Costagliola and Engels, 2010; Jianguang et al., 2010; Kristinsson et al., 2010; Lindqvist et al., 2011; K. Hemminki, Liu, Ji, et al., 2012a; Kari Hemminki, Liu, Forsti, et al., 2012; Kari Hemminki, Liu, Ji, et al., 2012; Hemminki et al., 2013; M. Fallah et al., 2014; Mahdi Fallah et al., 2014; Muller et al., 2014; Pfefiffer et al., 2015; Bellan et al., 2017)

Stage two

The second stage of composing the list of comorbidities that were included in this study involved augmenting the Charlson index with conditions for which there had been previously published research in PMR found as part of the systematic

review in chapter 5. These morbidities were in addition to those listed in the Charlson index.

Studies had previously been performed that looked for associations between PMR and thyroid disease, (Bowness et al., 1991; Juchet et al., 1993) Schizophrenia and other psychoses, (Eaton et al., 2006; Chen et al., 2012) all autoimmune conditions, (Eaton et al., 2007) Parkinson's disease, (Li, Sundquist and Sundquist, 2012) obesity, (Kari Hemminki, Li, et al., 2012) and overall mortality. (Gran et al., 2001; Doran et al., 2002; Uddhammar et al., 2002; Myklebust et al., 2003)

Of the conditions listed, in all but one there was sufficient clinical equipoise to be important to investigate, and so were included in the study. The single exception to this was obesity as it is not an outcome in itself, rather a risk factor for other conditions.

The comorbidities that were included, and the reasoning for the inclusion of each, are detailed in table 6-2.

Table 6-2: Additional comorbidities identified from systematic review

Disease groups	Condition	Rationale
Neurological	Parkinson's disease	Potentially similar presentation- stiffness/rigidity found in both conditions
Autoimmune, Rheumatological and Musculoskeletal	Systemic lupus erythematosus	As per Eaton et al. (2007)
	Systemic sclerosis	Assess likelihood of any connective tissue disease.
	Rheumatoid arthritis	Also assess for the presence of individual diseases.
	Sjogren's syndrome	
	Psoriatic arthritis	Many inflammatory rheumatological conditions may present with a polymyalgic picture and therefore be misdiagnosed.
	Raynaud's disease	
Endocrine	Thyroid disease	May share an autoimmune pathway
Psychiatric	Schizophrenia	May be linked to steroid usage
	Bipolar affective disorder	
Mortality	The Charlson index aims to predict mortality therefore is not part of the index; however useful to investigate formally.	

Many of the conditions listed above form part of the differential diagnosis of polymyalgia rheumatica. In fact, as discussed previously, it is explicit in clinical classification criteria that most of these conditions be excluded prior to making a diagnosis of PMR. (Dasgupta et al., 2010, 2012) Therefore it is important to know with what regularity these morbidities coexist with PMR. Furthermore, this would provide information on whether GPs are in fact adhering to guidelines used for the diagnosis of PMR. If they are, it is likely that in patients with PMR, a previous diagnosis with one of the conditions listed as exclusions, such as cancer, would be much less likely.

Stage three

Finally, the third stage in the identification of comorbidities that were assessed in this study involved discussion with experts in the diagnosis and management of PMR. These experts included three clinically and research active Consultant Rheumatologists, as well as discussion with two clinically active academic General Practitioners with extensive experience of co-ordinating studies on, and publishing results from, multiple research projects around the subject of PMR.

A number of recommendations were made. First, to expand the list of comorbidities to include conditions that could be side effects or a complication of long-term glucocorticoid (GC) treatment. The second recommendation was to include other extra-articular autoimmune conditions that may share a causative pathway with PMR. This hypothesis for this was that autoimmune diseases often coexist, for example rheumatoid arthritis and thyroid disease. (Somers et al., 2006)

The final recommendation was to, where possible, assess combined, or composite, outcomes as well as stratified comorbidities within disease categories. This meant combining outcomes from the final list of comorbidities into broad categories and assessing whether individuals had any event from within that category. The reason for this was to increase the sample size and therefore power to detect whether an effect exists. Some of the categories, for example autoimmune conditions, included conditions that are rarely diagnosed, therefore aggregating outcomes increased the statistical power of the test.

The additions to the list of comorbidities that were suggested by the expert group are detailed in table 6-3 and the final list of stratified individual comorbidities and composite outcomes are shown in tables 6-4 and 6-5.

Table 6-3: Comorbidities suggested following expert review

Disease group	**Condition**	**Rationale**
Vascular	Hypertension	Linked to steroid usage
Respiratory	Pulmonary fibrosis	Autoimmune condition
Rheumatological and Musculoskeletal	Osteoarthritis	Similar symptom profile
	Osteoporosis	Linked to steroid usage
	Hip fracture	
	Radius fracture	
	Vertebral fracture	
Gastroenterology	Inflammatory bowel diseases- IBD/Crohn's	Autoimmune conditions
Endocrine	Addison's disease	
	Type One Diabetes Mellitus	
Infectious Diseases	Urinary Tract Infection	Linked to impaired immunity and therefore steroid usage
	Upper Respiratory Tract Infection	
	Lower Respiratory Tract Infection	
	Cellulitis	
Ophthalmology	Cataracts	Linked to steroid usage
	Glaucoma	
Psychiatry	Depression	
	Anxiety	

Table 6-4: Final list of individual comorbidities for assessment

Disease Group	Condition	Disease Group	Condition	Disease Group	Condition
Vascular	Myocardial infarction	Respiratory	COPD	Gastroenterology	Peptic ulcer disease
	Congestive heart failure		*Chronic pulmonary disease* +		Moderate or severe liver disease
	Peripheral vascular disease		Asthma		Crohn's disease
			Pulmonary fibrosis		Ulcerative colitis
	Cerebrovascular accident	Endocrine	*Diabetes* +	Infectious Diseases	*Acquired immunodeficiency syndrome* +
	Hypertension		*Diabetes with chronic complications* +		Urinary Tract Infection *
Neurological	*Hemiplegia, paraplegia* +		Type 1 diabetes mellitus		Upper Respiratory Tract Infection *
	Dementia		Type 2 diabetes mellitus*		Lower Respiratory Tract Infection *
	Parkinson's disease		Hyperthyroidism		Cellulitis *
	Multiple sclerosis		Hypothyroidism		
Rheumatology and Musculoskeletal	Systemic Lupus Erythematosus		Addison's disease	Psychiatric	Schizophrenia
	Systemic sclerosis	Renal	Renal disease		Bipolar
	Rheumatoid Arthritis	Neoplastic	Breast cancer		Depression
	Sjogren's syndrome		Prostate cancer		Anxiety
	Psoriatic arthritis		Lung cancer	Ophthalmology	Cataracts *
	Raynaud's disease		Colorectal cancer		Glaucoma *
	Osteoarthritis		Melanoma		
	Osteoporosis *		Leukaemia, lymphoma		
	Hip fracture *		*Metastatic solid tumours* +		
	Radius fracture *		Any other cancer		
	Vertebral fracture *				

+ Only used in calculation of Charlson index * Prospective or related to GC dosage

Table 6-5: Composite comorbid outcomes for assessment

Disease Group	Outcomes included
Cancer	Breast, prostate, lung, colorectal, melanoma, leukaemia, lymphoma, or any other cancer
Vascular	Myocardial infarction, chronic heart failure, peripheral vascular disease, or cerebrovascular disease
Respiratory	Asthma, COPD, or lung fibrosis
Gastroenterological	Moderate liver disease, severe liver disease, peptic ulcers, Crohn's disease, or ulcerative colitis
Autoimmune	Systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, Sjogren's syndrome, psoriatic arthritis, or Raynaud's disease
Endocrine	Hyperthyroidism, hypothyroidism, type 1 diabetes mellitus, type 2 diabetes mellitus, or Addison's disease
Neurologic	Dementia, Parkinson's disease, or multiple sclerosis
Psychiatric	Schizophrenia, bipolar affective disorder, depression, or anxiety
Ophthalmology	Cataracts or glaucoma
Infections	Urinary tract infection, upper respiratory tract infection, lower respiratory tract infection, or skin infection
Fragility fractures	Hip fracture, wrist fracture, or vertebral fracture

Of this list of individual comorbidities, (table 6-4) not all the outcomes were individually reported. A small number of outcomes (n=6) are marked as only to be used as part of the Charlson index. There were two main reasons for excluding them from the main analysis. The first was in the case of conditions which are both rare and unlinked to autoimmune conditions, such as hemiplegia and paraplegia, which, following expert review, were not considered to have sufficient clinical equipoise. The second reason was where overlap exists between disease outcomes. For example, the Charlson index contains diabetes and diabetes with chronic complications; whereas following expert review it was felt more useful to assess the rates of type 1 and type 2 diabetes. In order that cases were not

counted multiple times, these comorbidities were used to calculate the Charlson index score but not reported individually.

One outcome was omitted from both the case control and cohort studies. This was mortality. Mortality cannot be included in the case control study, as it must occur prospectively following diagnosis. It is not included in the cohort study as, although CPRD does contain information about date of death, detailed information is only included as part of a linked database to which not all CPRD patients are part of. This database is the Office for National Statistics Death registration data and will be analysed in a later study (chapter 7). Finally, when there were very small numbers of patients (cell count <5) within a category the results were reported as (<5) to preserve patient anonymity.

The composite outcomes by disease groups (table 6-5) differs slightly to the individual outcomes listed in table 6-4, for example hypertension was not included as a vascular endpoint, as, although it is a disease in itself, it is not an outcome.

As discussed in chapter two, each Read code has a unique medical code to identify it in the CPRD database. The total number of medical codes used in this study was 7,164, and the process used to identify them was described in chapter 2.11.

6.2.8 Statistical analysis

Case Control analysis

For the case control study, conditional logistic regression was used to calculate the likelihood of a participant with or without PMR having previously been diagnosed with a comorbid disease. This likelihood will be expressed as an odds ratio with confidence intervals, which will be set at the 95% level. A confidence interval is an estimate of the values between which the true, population, value will lie. Setting the interval at 95% means there is a 1 in 20 chance of the true population mean lying outside these values. In the case of an odds ratio, if the confidence interval does not cross the value of 1, then the difference is regarded as being statistically significant. Furthermore, in addition to this, the width of a confidence interval provides further information on the precision of the estimate. (Prel et al., 2009)

Logistic regression was used as it is the method of choice for examining associations in case-control studies when the outcome is dichotomous: i.e. predicting whether a subject is a case or control. The output is expressed in terms of coefficients, which are interpreted as giving the change in the log of the odds of being a case, per unit change in the risk factor considered. Conditional logistic regression is a variant of logistic regression that also enables control for the effects of potentially confounding variables in addition to those used in matching. (Silman and Macfarlane, 2002) Conditional logistic analysis differs from regular logistic regression in that the data are grouped and the likelihood is calculated relative to each group; that is, a conditional likelihood is used. Unadjusted odds ratios were calculated as well as ratios adjusted for confounding variables. The covariates used to calculate adjusted ratios were smoking status, alcohol consumption and BMI category. The reference categories used for each of the

covariates in the conditional logistic model were non-smokers, no alcohol consumption and those with normal BMI.

Cohort analysis

For the cohort study, the Charlson index score and cumulative probability of the stratified and composite comorbidities were calculated at index date and four further time points following this. The time points were at one, two, five and ten years after index date. This follows the methods used by Kuo et al (2016). The cumulative probability of disease is defined as an estimate of the total number of patients with the comorbidity (numerator) divided by the total number of patients contributing data to the study during that time period (denominator). This method takes into account loss to follow up and also provides 95% confidence intervals.

Two functions are of particular interest when analysing study data, which is dependent on time. These are the cumulative survival function S(t) and the hazard function h(t). These functions can be broadly regarded as inverse to each other, in that S(t) is the probability of surviving without developing the condition up to the time-point t, while h(t) is the probability of developing it at that time having survived to without developing it up to that point. In this study the h(t), the cumulative probability of comorbid disease development, and time to development of each comorbidity will be reported.

In order to assess the likelihood of prospectively developing a comorbidity in the cohort study, the Cox regression model was utilised. This is also known as proportional hazards regression, because of the assumptions required to fit this

model. This model is used when the time to the development of an event, “survival time”, is the outcome of interest. Predictor variables can be binary, categorical or continuous. (Silman and Macfarlane, 2002)

Survival time was initially synonymous with survival until death, however the technique has been extended to include time until a particular event, in this case development of a comorbidity. The model was used to calculate hazard ratios (HRs) for the likelihood of comorbidity in exposed (patients with PMR) compared to non-exposed (patients without PMR) groups. As in the logistic regression model used in the case control analysis, the hazard ratios were calculated unadjusted as well as adjusted, for smoking status, alcohol consumption and body mass index (BMI) category with 95% significance levels. In addition to these covariates, and in contrast to the conditional logistic regression, the hazard ratios were also adjusted for the matching variables age and sex, as the Cox model does not inherently account for the matched study design.

Using Cox regression model is superior to simple analysis such as the average (mean) survival time for a number of reasons. Firstly, survival data is rarely distributed Normally therefore simple methods would give an incomplete picture. Furthermore, Cox regression is able to take into account differential amounts of follow up. It is inevitable during a prolonged follow up period that not all study participants will experience an event prior to the end of the study period. These patients, who are ‘lost to follow up’ for a number of different reasons, as discussed in chapter 6.2.5, are taken into account by Cox regression.

Kaplan-Meier methods (Kaplan and Meier, 1958) are an effective way of estimating survival, or time without development of condition of interest.

However, it is limited to univariate analysis and therefore covariates or potential confounding factors cannot be included in the model. The Cox regression model (Cox, 1972) is superior in that multiple potential explanatory covariates, or confounders, can be included in the model to assess their influence on the likelihood of developing an event of interest over time.

However, there are several assumptions that underpin Cox regression model:

1) The first assumption is that the baseline hazard function is constant and common to all subjects in all of the comparison groups. The hazard function, i.e. the risk of developing the event of interest, for each group is the product of this baseline hazard and the predictors, or covariates. Thus, the covariates do not act on the baseline hazard function, only on the subsequent group-specific hazard function.
2) The second assumption is that of proportional hazards, i.e. that the hazard ratio does not vary with time following index date. This assumption means that if the risk of developing a comorbidity in the exposed group is 50% higher than in the non-exposed group, then this excess risk will remain the same throughout the study period.
3) The third assumption is that the censoring of data is non-informative, that is to say it is independent of the outcome. For example, in this study, there was no requirement for a specific follow up time after the index date. This was to prevent the exclusion of patients where the reason for their leaving the study was associated with an outcome of interest. For example if they died due to a myocardial infarct soon after index date

Finally, in order to test whether the hazards remain proportional, i.e. do not vary over time, Kaplan Meier methods were used to graphically plot and visualise the survival estimates over time. Furthermore, the models were fitted with robust standard errors, which offer greater resistance to outliers. (Huber, 1972)

When calculating hazard ratios and Kaplan-Meier plots to describe the likelihood of a diagnosis with a comorbidity, all patients with a pre-existing diagnosis with that comorbidity were excluded from the analysis. This was to ensure the likelihood measure reported was of incident diagnosis following index date rather than the likelihood of, or time until, a patient had another record of a comorbidity in their EHR. This meant that each comorbidity had different denominators, these were calculated and reported.

6.3 Results

6.3.1 Study demographics

A total of 5.3 million patients who were actively contributing data to CPRD and aged over 40 during the study period were initially included in this study. From this initial sample, 42,145 PMR cases were identified, as described in chapter 4. Of these, 31,984 (75.9%) were matched to 149,436 controls, who fulfilled the previously outlined matching criteria. If a case had two or fewer matched controls, neither the cases nor controls were included. Demographic data collected for each patient included mean age at index date, sex, region of GP practice, smoking status, BMI category, alcohol consumption and the total time each patient actively contributed data to the study. The time each patient contributed was also stratified to before and after index date. This data is presented in table 6-6.

Table 6-6: Demographic information for comorbidities study

	Total	Cases	Controls
Observations	181,420	31,984	149,436
Age at diagnosis (years)			
Mean (SD)	73.4 (8.9)	73.7 (9.0)	73.3 (8.8)
Min / Max	43.0 / 100.3	43.0 / 100.3	43.0 / 99.8
Sex (%)			
Male	58,818 (32.4)	10,596 (33.1)	48,222 (32.3)
Female	122,602 (67.6)	21,388 (66.9)	101,214 (67.7)
Region (%)			
North East	2,307 (1.3)	404 (1.3)	1,903 (1.3)
North West	17,681 (9.7)	3,108 (9.7)	14,573 (9.8)
Yorkshire & the Humber	5,376 (3.0)	964 (3.0)	4,412 (3.0)
East Midlands	6,624 (3.7)	1,151 (3.6)	5,473 (3.7)
West Midlands	18,967 (10.5)	3,297 (10.3)	15,670 (10.5)
East of England	19,878 (11.0)	3,458 (10.8)	16,420 (11.0)
South West	19,991 (11.0)	3,530 (11.0)	16,461 (11.0)
South Central	19,958 (11.0)	3,545 (11.1)	16,413 (11.0)
London	11,028 (6.1)	2,044 (6.4)	8,984 (6.0)
South East Coast	21,574 (11.9)	3,823 (12.0)	17,751 (11.9)
Northern Ireland	4,757 (2.6)	822 (2.6)	3,935 (2.6)
Scotland	13,954 (7.7)	2,475 (7.7)	11,479 (7.7)
Wales	19,325 (10.7)	3,363 (10.5)	15,962 (10.7)
Total time at risk			
Mean (SD)	14.8 (5.5)	15.6 (5.4)	14.7 (5.5)
Min / Max	3.0 / 27.0	3.2 / 27.0	3.0 / 27.0
Pre-index date time at risk			
Mean (SD)	9.9 (5.0)	10.2 (5.1)	9.8 (5.0)
Min / Max	3.0 / 26.9	3.0 / 26.9	3.0 / 26.9
Post-index date time at risk			
Mean (SD)	5.0 (3.9)	5.4 (4.0)	4.9 (3.9)
Min / Max	0.0 / 24.0	0.0 / 23.7	0.0 / 24.0
BMI category (%)			
Normal (18.5-24.9)	57,080 (31.5)	9,998 (31.3)	47,082 (31.5)
Underweight (<18.5)	3,291 (1.8)	401 (1.3)	2,890 (1.9)
Overweight (25-29.9)	61,072 (33.7)	11,605 (36.3)	49,467 (33.1)
Obese (>=30)	36,309 (20.0)	6,884 (21.5)	29,425 (19.7)
Missing	23,668 (13.0)	3,096 (9.7)	20,572 (13.8)
Smoking (%)			
Never/ex-smoker	149,851 (82.6)	27,603 (86.3)	122,248 (81.8)
Smoker	21,070 (11.6)	3,218 (10.1)	17,852 (11.9)
Missing	10,499 (5.8)	1,163 (3.6)	9,336 (6.2)
Alcohol (%)			
Never/ex drinker	38,397 (21.2)	6,714 (21.0)	31,683 (17.5)
<10 units per week	93,227 (51.4)	17,256 (54.0)	75,971 (41.9)
10 or more units per week	24,997 (13.8)	4,551 (14.2)	20,446 (11.3)
Missing	24,799 (13.7)	3,463 (10.8)	21,336 (11.8)

The average age at diagnosis, sex and region of GP practice were similar for both cases and controls, reflecting the matching criteria that were applied. Furthermore, the average age of the matched cases (73.7 years) was also almost identical to the mean age of cases in chapter 4 (73.8 years). This indicates that the matching process did not change the average age of study participants. The average length of time each patient contributed to the study was slightly different. The overall mean observation period was 14.8 years [standard deviation (SD) 5.52], however for cases this figure was 15.6 years [SD 5.4] and for controls this was 14.7 years [SD 5.5].

The three disease risk modifiers, BMI, smoking and alcohol consumption, were broadly similar between cases and controls. The main points of difference were that the data was more likely to be recorded in cases compared to controls for all the covariates. Furthermore, a higher proportion of cases were recorded as drinking greater than 10 units of alcohol per week (14.2% vs 11.3%). However, in the case of smoking, this situation was reversed and patients from the control group were more likely to be recorded as smokers in comparison to cases (10.1% vs 11.9%).

6.3.2 Case control study

Due to the large number of outcomes reported in this study, a number of abbreviations have been used in the table to improve formatting. The abbreviations are shown in table 6-7.

Table 6-7: Abbreviations for comorbid outcomes

Comorbidity	Abbreviation
Leukaemia, lymphoma	LL
Cardiovascular disease	CVD
Congestive cardiac failure	CCF
Peripheral vascular disease	PVD
Cerebrovascular disease	CVA
Hypertension	HTN
Chronic obstructive pulmonary disease	COPD
Ulcerative colitis	UC
Systemic lupus erythematosus	SLE
Rheumatoid arthritis	RA
Osteoarthritis	OA
Type 1 Diabetes mellitus	T1DM
Type 2 Diabetes mellitus	T2DM
Multiple sclerosis	MS
Urinary tract infection	UTI
Upper respiratory tract infection	URTI
Lower respiratory tract infection	LRTI

The case control study included data on the prevalence of comorbidities in patients with PMR compared to their matched controls at three time points prior to index date (five years, two years and one year). The overall comorbidity burden that cases and controls were subjected to was estimated using the Charlson index score. The number, and proportion, of patients with each score were reported. Due to small numbers, all patients with a Charlson score of greater than 5 were aggregated. The composite outcomes and Charlson index scores are summarised in table 6-8.

Table 6-8: Prevalence of composite outcomes and Charlson Index score (total number of cases and %) at specified time points prior to index date

	5y		2y		1y	
Charlson score	**Case**	**Control**	**Case**	**Control**	**Case**	**Control**
0	13,640 (51.2)	65,882 (54.5)	13,952 (43.6)	70,405 (47.1)	12,974 (40.6)	66,094 (44.2)
1	6,718 (25.2)	27,607 (22.8)	7,953 (24.9)	33,699 (22.6)	7,776 (24.3)	33,216 (22.2)
2	3,667 (13.8)	15,716 (13.0)	5,125 (16.0)	23,278 (15.6)	5,421 (16.9)	24,431 (16.3)
3	1,595 (6.0)	6,959 (5.8)	2,650 (8.3)	11,631 (7.8)	2,979 (9.3)	12,974 (8.7)
4	649 (2.4)	2,880 (2.4)	1,315 (4.1)	5,676 (3.8)	1,542 (4.8)	6,645 (4.4)
5	231 (0.9)	1,089 (0.9)	602 (1.9)	2,671 (1.8)	763 (2.4)	3,272 (2.2)
Greater than 5	133 (0.5)	736 (0.6)	387 (1.2)	2,076 (1.4)	529 (1.7)	2,804 (1.9)
Composite outcomes						
Cancer	2,118 (8.0)	10,246 (8.5)	3,287 (10.3)	16,455 (11.0)	3,627 (11.3)	18,233 (12.2)
Vascular	4,964 (18.6)	21,065 (17.4)	7,443 (23.3)	32,462 (21.7)	8,003 (25.0)	34,888 (23.3)
Respiratory	5,525 (20.7)	20,952 (17.3)	7,387 (23.1)	28,888 (19.3)	7,754 (24.2)	30,189 (20.2)
Gastroenterological	1,621 (6.1)	7,060 (5.8)	2,211 (6.9)	9,706 (6.5)	2,325 (7.3)	10,091 (6.8)
Immunological	1,212 (4.6)	4,445 (3.7)	1,728 (5.4)	6,278 (4.2)	1,874 (5.9)	6,659 (4.5)
Endocrine	4,778 (17.9)	19,116 (15.8)	6,814 (21.3)	28,260 (18.9)	7,297 (22.8)	30,066 (20.1)
Neurological	178 (0.7)	1,912 (1.6)	318 (1.0)	4,106 (2.7)	397 (1.2)	4,973 (3.3)
Psychiatric	5,700 (21.4)	23,398 (19.4)	7,375 (23.1)	31,208 (20.9)	7,666 (24.0)	32,381 (21.7)
Ophthalmological	2,519 (9.5)	10,208 (8.4)	3,620 (11.3)	14,573 (9.8)	4,061 (12.7)	16,203 (10.8)
Infections	15,415 (57.9)	62,948 (52.1)	18,043 (56.4)	74,643 (49.9)	18,754 (58.6)	77,799 (52.1)
Fragility fractures	1,342 (5.0)	6,337 (5.2)	1,592 (5.0)	7,685 (5.1)	1,701 (5.3)	8,208 (5.5)

Charlson Index

Overall comorbidity burden, as measured by Charlson comorbidity index, was found to be higher prior to index date in cases compared to controls. A higher proportion of controls had a Charlson score of zero at all three time points when compared to cases (5y: 54.5% vs 51.2%, 2y: 47.1% vs 43.6% and 1y: 44.2% vs 40.6%). Furthermore, the proportion of cases who had a Charlson index score of 1-5 was higher at all three time points when compared to controls. However, although the numbers were small, a smaller proportion of cases had a Charlson index score greater than five compared to controls.

Composite Outcomes

In eight of the combined categories (vascular, respiratory, gastroenterological, immunological, endocrine, psychiatric, ophthalmological and infectious diseases) the prevalence of existing disease was higher in cases compared to controls at all three time points prior to index date. Conversely, three categories were associated with a reduced prevalence of comorbid disease in cases compared to controls at each time point prior to index date. These categories were cancer, neurological diseases and fragility fractures. Of the outcomes that could be related to GC therapy, two were higher in the case group (ophthalmologic diseases and infections), while one (fragility fractures) were more prevalent among controls. To look into further detail of these findings, the stratified outcomes are summarised in table 6-9.

Table 6-9: Prevalence of stratified comorbidities at specified time points prior to index date (total number of cases and %)

	5y		**2y**		**1y**	
	Case	Control	Case	Control	Case	Control
Cancer						
Breast cancer	600 (2.3)	2,943 (2.4)	823 (2.6)	4,418 (3.0)	875 (2.7)	4,758 (3.2)
Prostate cancer	160 (0.6)	805 (0.7)	320 (1.0)	1,512 (1.0)	380 (1.2)	1,747 (1.2)
Lung cancer	22 (0.1)	135 (0.1)	45 (0.1)	261 (0.2)	57 (0.2)	357 (0.2)
Colon cancer	207 (0.8)	1,014 (0.8)	327 (1.0)	1,650 (1.1)	378 (1.2)	1,870 (1.3)
Melanoma	187 (0.7)	845 (0.7)	273 (0.9)	1,241 (0.8)	297 (0.9)	1,336 (0.9)
LL	111 (0.4)	684 (0.6)	190 (0.6)	1,241 (0.8)	205 (0.6)	1,397 (0.9)
Vascular						
CVD	3,437 (12.9)	13,656 (11.3)	4,909 (15.3)	19,976 (13.4)	5,193 (16.2)	21,123 (14.1)
CCF	644 (2.4)	2,763 (2.3)	1,203 (3.8)	5,356 (3.6)	1,403 (4.4)	6,196 (4.1)
PVD	712 (2.7)	3,091 (2.6)	1,146 (3.6)	5,159 (3.5)	1,286 (4.0)	5,701 (3.8)
CVA	1,221 (4.6)	6,203 (5.1)	2,085 (6.5)	10,542 (7.1)	2,344 (7.3)	11,700 (7.8)
HTN	10,664 (40.0)	45,133 (37.3)	14,921 (46.7)	64,312 (43.0)	15,711 (49.1)	67,636 (45.3)
Respiratory						
Asthma	3,510 (13.2)	12,927 (10.7)	4,713 (14.7)	17,630 (11.8)	4,898 (15.3)	18,327 (12.3)
COPD	2,873 (10.8)	11,330 (9.4)	4,017 (12.6)	16,365 (11.0)	4,310 (13.5)	17,450 (11.7)
Lung fibrosis	64 (0.2)	223 (0.2)	124 (0.4)	405 (0.3)	166 (0.5)	483 (0.3)
Renal						
Renal disease	1,092 (4.1)	4,539 (3.8)	2,686 (8.4)	11,027 (7.4)	3,362 (10.5)	13,653 (9.1)
Gastroenterological						
Liver disease	157 (0.6)	837 (0.7)	239 (0.7)	1,302 (0.9)	270 (0.8)	1,426 (1.0)
Peptic ulcers	1,131 (4.2)	4,898 (4.1)	1,501 (4.7)	6,608 (4.4)	1,552 (4.9)	6,800 (4.6)
Crohn's disease	74 (0.3)	353 (0.3)	100 (0.3)	490 (0.3)	107 (0.3)	505 (0.3)
UC	315 (1.2)	1,176 (1.0)	447 (1.4)	1,611 (1.1)	479 (1.5)	1,691 (1.1)
Autoimmune and musculoskeletal						
SLE	24 (0.1)	129 (0.1)	37 (0.1)	182 (0.1)	38 (0.1)	190 (0.1)
Systemic sclerosis	21 (0.1)	58 (0.0)	21 (0.1)	89 (0.1)	23 (0.1)	93 (0.1)
RA	694 (2.6)	2,666 (2.2)	971 (3.0)	3,719 (2.5)	1,041 (3.3)	3,914 (2.6)
Sjogren’s syndrome	57 (0.2)	188 (0.2)	91 (0.3)	282 (0.2)	98 (0.3)	311 (0.2)
Psoriatic arthritis	116 (0.4)	361 (0.3)	160 (0.5)	529 (0.4)	173 (0.5)	565 (0.4)
Raynaud's disease	297 (1.1)	1,118 (0.9)	445 (1.4)	1,649 (1.1)	501 (1.6)	1,786 (1.2)
Osteoarthritis	10,009 (37.6)	38,092 (31.5)	13,888 (43.4)	53,979 (36.1)	14,776 (46.2)	57,048 (38.2)

	5y		2y		1y	
	Case	Control	Case	Control	Case	Control
Endocrine						
Hyperthyroidism	509 (1.9)	2,049 (1.7)	678 (2.1)	2,810 (1.9)	698 (2.2)	2,936 (2.0)
Hypothyroidism	2,433 (9.1)	8,097 (6.7)	3,424 (10.7)	11,884 (8.0)	3,670 (11.5)	12,665 (8.5)
T1DM	144 (0.5)	619 (0.5)	190 (0.6)	858 (0.6)	198 (0.6)	902 (0.6)
T2DM	1,684 (6.3)	8,235 (6.8)	2,672 (8.4)	13,104 (8.8)	2,938 (9.2)	14,252 (9.5)
Addison's disease	13 (0.0)	42 (0.0)	18 (0.1)	62 (0.0)	20 (0.1)	68 (0.0)
Neurological						
Dementia	20 (0.1)	532 (0.4)	78 (0.2)	1,936 (1.3)	132 (0.4)	2,651 (1.8)
Parkinson's disease	74 (0.3)	623 (0.5)	133 (0.4)	1,232 (0.8)	158 (0.5)	1,419 (0.9)
MS	46 (0.2)	347 (0.3)	59 (0.2)	453 (0.3)	60 (0.2)	456 (0.3)
Psychiatric						
Schizophrenia	38 (0.1)	464 (0.4)	53 (0.2)	648 (0.4)	53 (0.2)	666 (0.4)
Bipolar disease	36 (0.1)	232 (0.2)	57 (0.2)	345 (0.2)	58 (0.2)	358 (0.2)
Depression	4,334 (16.3)	17,607 (14.6)	5,623 (17.6)	23,676 (15.8)	5,862 (18.3)	24,597 (16.5)
Anxiety	3,088 (11.6)	12,636 (10.5)	4,034 (12.6)	17,001 (11.4)	4,226 (13.2)	17,736 (11.9)
Complications due to glucocorticoids						
Osteoporosis	1,205 (4.5)	4,949 (4.1)	2,061 (6.4)	8,728 (5.8)	2,349 (7.3)	9,882 (6.6)
Hip fracture	139 (0.5)	912 (0.8)	258 (0.8)	1,854 (1.2)	307 (1.0)	2,186 (1.5)
Wrist fracture	1,200 (4.5)	5,389 (4.5)	1,621 (5.1)	7,534 (5.0)	1,705 (5.3)	7,919 (5.3)
Vertebral fracture	33 (0.1)	198 (0.2)	59 (0.2)	326 (0.2)	71 (0.2)	363 (0.2)
Ophthalmological						
Cataracts	1,629 (6.1)	6,455 (5.3)	2,968 (9.3)	11,955 (8.0)	3,400 (10.6)	13,629 (9.1)
Glaucoma	1,059 (4.0)	4,455 (3.7)	1,638 (5.1)	7,029 (4.7)	1,800 (5.6)	7,620 (5.1)
Infections						
UTI	3,778 (14.2)	15,417 (12.8)	5,417 (16.9)	22,534 (15.1)	5,848 (18.3)	24,518 (16.4)
URTI	13,692 (51.4)	54,512 (45.1)	18,248 (57.1)	74,708 (50.0)	19,227 (60.1)	78,927 (52.8)
LRTI	649 (2.4)	2,733 (2.3)	973 (3.0)	4,091 (2.7)	1,061 (3.3)	4,407 (2.9)
Skin infections	2,366 (8.9)	9,685 (8.0)	3,578 (11.2)	15,261 (10.2)	3,991 (12.5)	16,993 (11.4)

Abbreviations: Leukaemia, lymphoma (LL), Cardiovascular disease (CVD), Congestive cardiac failure (CCF), Peripheral vascular disease (PVD), Cerebrovascular disease (CVA), Hypertension (HTN), Chronic obstructive pulmonary disease (COPD), Ulcerative colitis (UC), systemic lupus erythematosus (SLE), Rheumatoid arthritis (RA), Osteoarthritis (OA), Type 1 Diabetes mellitus (T1DM), Type 2 Diabetes mellitus (T2DM), Multiple sclerosis (MS), Urinary tract infection (UTI), Upper respiratory tract infection (URTI), Lower respiratory tract infection (LRTI)

Stratified outcomes

When outcomes were stratified into individual comorbidities, the patterns present were broadly similar to composite outcomes, however there were some exceptions.

Cancer

In all but one of the stratified comorbidities, the prevalence of cancer was higher in controls compared to cases, albeit the differences were small. The single comorbidity in which this did not occur was melanoma, a type of skin cancer. In this case, the prevalence was similar at 5 and 1 years prior to index date and slightly higher among cases (0.9% vs 0.8%) two years prior to index date.

Vascular

A higher prevalence of vascular disease was seen among cases compared to controls. However, cerebrovascular disease bucked this trend and was actually slightly more prevalent in controls rather than cases. This difference persisted throughout each time point (5y: 5.1% vs 4.6%, 2y: 7.1% vs 6.5% and 1y: 7.8% vs 7.3%). However, the prevalence of other measured vascular outcomes, such as cardiovascular and peripheral vascular disease was higher at every time point among cases when compared to controls.

Other comorbidities

All the stratified respiratory, autoimmune and musculoskeletal outcomes, including asthma, COPD, lung fibrosis, SLE, systemic sclerosis, rheumatoid arthritis, Sjogren's disease, psoriatic arthritis, Raynaud's disease and osteoarthritis, had higher prevalence in cases compared to controls.

There was some divergence between composite and stratified outcomes in the case of gastroenterological, endocrine and psychiatric diagnoses. Despite the fact that, overall, these diagnoses had a higher prevalence in cases compared to controls, it was found that in the stratified outcomes of liver disease, type two diabetes, schizophrenia and bipolar disease, that prevalence was actually higher in controls. In the case of neurological outcomes, all were more common in controls when compared to cases.

Comorbidities linked to GC prescription

Although this study looked retrospectively, prior to diagnosis with PMR, the risk of comorbidities that were linked to GC therapy were also included. Within these, the proportion of patients who developed each type of infectious and ophthalmological comorbidity was higher among cases when compared to controls. Regarding the risk of fracture, the picture was more mixed. Although the proportion of patients with a diagnosis of osteoporosis was greater among cases when compared to controls, the proportion who had a recorded hip fracture was lower in cases. The proportion who had a record of either a wrist or vertebral fracture was similar between cases and controls.

In order to ascertain whether these differences in prevalence of comorbidities in patients with PMR and their matched controls is significantly different, conditional logistic regression was used to calculate odds ratios with 95% confidence intervals (both crude and adjusted for BMI category, sex, smoking status and alcohol consumption). The results of the composite outcomes are summarised in table 6-10.

Table 6-10: Odds ratios (with 95% confidence intervals) PMR vs controls of composite outcomes at time points prior to index date calculated using conditional logistic regression

	5y		**2y**		**1y**	
	Unadjusted odds ratio	**Adjusted odds ratio**	**Unadjusted odds ratio**	**Adjusted odds ratio**	**Unadjusted odds ratio**	**Adjusted odds ratio**
Cancer	0.92 (0.87,0.97)	0.91 (0.86,0.95)	0.91 (0.88,0.95)	0.90 (0.87,0.94)	0.91 (0.87,0.94)	0.89 (0.86,0.93)
Vascular	1.05 (1.02,1.09)	1.03 (0.99,1.07)	1.07 (1.04,1.10)	1.04 (1.01,1.07)	1.07 (1.04,1.10)	1.04 (1.01,1.07)
Respiratory	1.25 (1.20,1.29)	1.22 (1.18,1.26)	1.26 (1.22,1.30)	1.23 (1.20,1.27)	1.27 (1.23,1.31)	1.24 (1.21,1.28)
Gastroenterological	1.03 (0.97,1.09)	1.03 (0.97,1.09)	1.06 (1.01,1.11)	1.05 (1.00,1.10)	1.07 (1.02,1.12)	1.06 (1.02,1.12)
Autoimmune	1.25 (1.17,1.33)	1.23 (1.15,1.31)	1.31 (1.24,1.38)	1.29 (1.22,1.36)	1.34 (1.27,1.42)	1.32 (1.25,1.39)
Endocrine	1.17 (1.13,1.21)	1.14 (1.10,1.18)	1.17 (1.13,1.20)	1.13 (1.10,1.17)	1.18 (1.15,1.22)	1.14 (1.11,1.18)
Neurological	0.40 (0.34,0.47)	0.41 (0.35,0.48)	0.34 (0.30,0.38)	0.35 (0.31,0.39)	0.35 (0.31,0.39)	0.36 (0.32,0.40)
Psychiatric	1.16 (1.13,1.21)	1.16 (1.12,1.20)	1.16 (1.12,1.19)	1.15 (1.12,1.19)	1.16 (1.13,1.20)	1.15 (1.12,1.19)
Ophthalmological	1.08 (1.03,1.13)	1.06 (1.01,1.12)	1.10 (1.06,1.15)	1.08 (1.04,1.13)	1.18 (1.13,1.22)	1.15 (1.11,1.20)
Infections	1.33 (1.29,1.37)	1.29 (1.25,1.33)	1.36 (1.32,1.40)	1.31 (1.27,1.35)	1.44 (1.40,1.49)	1.39 (1.35,1.43)
Fragility fractures	0.95 (0.89,1.01)	0.94 (0.89,1.01)	0.92 (0.87,0.98)	0.92 (0.87,0.97)	0.96 (0.91,1.01)	0.95 (0.90,1.01)

Composite outcomes

The results of conditional logistic regression analysis, which aimed to investigate the differences in prevalence between comorbidities in patients with and without PMR, found that many of the differences in prevalence of comorbidities previously described were statistically significant. For a number of combined outcomes almost all of the calculated odds ratios at each of the three time points prior to index date showed a significant increase in the likelihood of having pre-existing disease in patients with PMR. These outcomes included vascular, respiratory, gastroenterological, immunological, endocrine, psychiatric ophthalmological and infectious diseases.

These findings mirror the increased prevalence of these conditions in patients with PMR compared to matched controls previously demonstrated and persisted following adjustment for BMI, smoking status and alcohol consumption. Similarly, in the case of cancers and neurological diseases, where a reduced prevalence of disease in patients with PMR had been seen, the differences were also found to be statistically significant. Finally, although the likelihood of patients with PMR having a recorded fragility fracture was significantly lower two years prior to index date, the differences observed at one and five years prior to index date were not significantly different.

The stratified outcomes are tabulated in table 6-11. They are also graphically presented in figures 6-1 and 6-2 to allow for ease of interpretation. On these figures, the total number of patients with PMR who were diagnosed with each condition is also indicated.

Table 6-11: Odds ratios (with 95% confidence intervals) PMR vs controls of stratified outcomes at time points prior to index date calculated using conditional logistic regression

	5y Unadjusted odds ratio	Adjusted odds ratio	2y Unadjusted odds ratio	Adjusted odds ratio	1y Unadjusted odds ratio	Adjusted odds ratio
Cancer						
Breast cancer	0.93 (0.85,1.02)	0.92 (0.84,1.01)	0.88 (0.81,0.95)	0.87 (0.81,0.94)	0.86 (0.80,0.93)	0.86 (0.80,0.92)
Prostate cancer	0.85 (0.71,1.01)	0.84 (0.70,1.00)	0.94 (0.83,1.07)	0.93 (0.82,1.05)	0.97 (0.86,1.09)	0.95 (0.85,1.07)
Lung cancer	0.69 (0.44,1.09)	0.68 (0.43,1.08)	0.78 (0.57,1.07)	0.77 (0.56,1.06)	0.73 (0.55,0.97)	0.72 (0.54,0.95)
Colon cancer	0.90 (0.77,1.05)	0.89 (0.77,1.04)	0.90 (0.80,1.02)	0.89 (0.79,1.00)	0.92 (0.82,1.03)	0.91 (0.81,1.01)
Melanoma	1.01 (0.86,1.19)	0.99 (0.85,1.17)	1.02 (0.89,1.16)	1.00 (0.88,1.14)	1.03 (0.90,1.16)	1.01 (0.89,1.14)
LL	0.73 (0.60,0.90)	0.72 (0.59,0.88)	0.71 (0.61,0.82)	0.70 (0.60,0.81)	0.68 (0.58,0.78)	0.67 (0.58,0.77)
Vascular						
CVD	1.13 (1.09,1.18)	1.10 (1.05,1.15)	1.16 (1.12,1.20)	1.11 (1.07,1.15)	1.16 (1.12,1.20)	1.12 (1.08,1.16)
CCF	1.01 (0.92,1.11)	0.99 (0.91,1.09)	1.01 (0.94,1.07)	0.98 (0.92,1.05)	1.01 (0.95,1.08)	0.99 (0.93,1.05)
PVD	1.01 (0.93,1.10)	1.02 (0.93,1.11)	1.01 (0.95,1.08)	1.01 (0.94,1.08)	1.03 (0.97,1.10)	1.03 (0.97,1.10)
CVA	0.86 (0.80,0.91)	0.85 (0.79,0.90)	0.89 (0.85,0.93)	0.88 (0.83,0.92)	0.90 (0.86,0.94)	0.89 (0.85,0.93)
HTN	1.11 (1.08,1.14)	1.06 (1.03,1.09)	1.17 (1.14,1.20)	1.11 (1.08,1.14)	1.18 (1.15,1.21)	1.12 (1.09,1.15)
Respiratory						
Asthma	1.27 (1.22,1.32)	1.24 (1.19,1.29)	1.30 (1.26,1.35)	1.26 (1.22,1.31)	1.30 (1.26,1.35)	1.27 (1.22,1.31)
COPD	1.16 (1.11,1.21)	1.15 (1.10,1.20)	1.17 (1.12,1.21)	1.16 (1.11,1.20)	1.18 (1.13,1.22)	1.17 (1.12,1.21)
Lung fibrosis	1.28 (0.96,1.69)	1.24 (0.94,1.65)	1.42 (1.16,1.74)	1.38 (1.13,1.70)	1.60 (1.34,1.91)	1.56 (1.31,1.87)
Renal						
Renal disease	1.06 (0.99,1.14)	1.04 (0.97,1.12)	1.15 (1.10,1.21)	1.13 (1.07,1.18)	1.18 (1.12,1.23)	1.15 (1.10,1.20)
Gastroenterological						
Liver disease	0.85 (0.71,1.01)	0.85 (0.71,1.01)	0.86 (0.75,0.99)	0.85 (0.74,0.98)	0.89 (0.78,1.01)	0.88 (0.77,1.01)
Peptic ulcers	1.03 (0.96,1.10)	1.03 (0.96,1.10)	1.04 (0.99,1.11)	1.04 (0.99,1.11)	1.05 (0.99,1.11)	1.05 (0.99,1.11)
Crohn's disease	0.99 (0.77,1.28)	0.98 (0.76,1.27)	0.97 (0.78,1.20)	0.96 (0.78,1.20)	1.01 (0.82,1.24)	1.00 (0.81,1.23)

	5y Unadjusted odds ratio	Adjusted odds ratio	2y Unadjusted odds ratio	Adjusted odds ratio	1y Unadjusted odds ratio	Adjusted odds ratio
Ulcerative colitis	1.22 (1.08,1.39)	1.19 (1.05,1.35)	1.31 (1.18,1.46)	1.28 (1.15,1.42)	1.33 (1.20,1.48)	1.30 (1.18,1.45)
Autoimmune and musculoskeletal						
SLE	0.88 (0.57,1.37)	0.88 (0.57,1.36)	0.97 (0.68,1.38)	0.96 (0.67,1.37)	0.95 (0.67,1.34)	0.94 (0.67,1.34)
Systemic sclerosis	1.73 (1.04,2.86)	1.71 (1.03,2.84)	1.12 (0.69,1.80)	1.13 (0.70,1.82)	1.18 (0.74,1.86)	1.19 (0.75,1.88)
Rheumatoid arthritis	1.17 (1.07,1.28)	1.16 (1.07,1.27)	1.22 (1.14,1.32)	1.21 (1.13,1.30)	1.25 (1.17,1.34)	1.24 (1.15,1.33)
Sjogren’s syndrome	1.44 (1.07,1.95)	1.40 (1.04,1.90)	1.53 (1.21,1.94)	1.48 (1.17,1.88)	1.50 (1.19,1.89)	1.45 (1.16,1.83)
Psoriatic arthritis	1.47 (1.19,1.82)	1.45 (1.17,1.79)	1.42 (1.19,1.70)	1.39 (1.16,1.67)	1.44 (1.21,1.71)	1.40 (1.18,1.67)
Raynaud's disease	1.22 (1.07,1.39)	1.20 (1.05,1.37)	1.28 (1.15,1.42)	1.25 (1.12,1.39)	1.33 (1.20,1.47)	1.30 (1.18,1.44)
Osteoarthritis	1.33 (1.29,1.37)	1.30 (1.26,1.34)	1.39 (1.36,1.43)	1.36 (1.32,1.39)	1.43 (1.39,1.47)	1.39 (1.35,1.43)
Endocrine						
Hyperthyroidism	1.14 (1.04,1.26)	1.14 (1.03,1.26)	1.14 (1.05,1.24)	1.13 (1.04,1.24)	1.13 (1.03,1.22)	1.12 (1.03,1.22)
Hypothyroidism	1.43 (1.36,1.50)	1.40 (1.34,1.47)	1.41 (1.36,1.47)	1.39 (1.33,1.44)	1.43 (1.37,1.49)	1.40 (1.34,1.46)
T1DM	1.06 (0.88,1.27)	1.02 (0.85,1.23)	1.05 (0.89,1.23)	1.00 (0.85,1.17)	1.04 (0.89,1.21)	0.99 (0.85,1.16)
T2DM	0.91 (0.86,0.96)	0.88 (0.83,0.93)	0.94 (0.90,0.99)	0.90 (0.86,0.94)	0.95 (0.91,1.00)	0.91 (0.88,0.95)
Addison's disease	1.42 (0.76,2.68)	1.41 (0.75,2.65)	1.35 (0.79,2.29)	1.33 (0.78,2.26)	1.37 (0.83,2.26)	1.35 (0.82,2.24)
Neurological and psychiatric						
Dementia	0.15 (0.10,0.24)	0.16 (0.10,0.25)	0.17 (0.13,0.21)	0.17 (0.14,0.22)	0.21 (0.18,0.25)	0.22 (0.18,0.26)
Parkinson's disease	0.51 (0.40,0.66)	0.51 (0.40,0.65)	0.49 (0.41,0.59)	0.49 (0.41,0.58)	0.51 (0.43,0.60)	0.50 (0.43,0.60)
MS	0.62 (0.46,0.85)	0.64 (0.47,0.87)	0.63 (0.48,0.82)	0.65 (0.49,0.85)	0.63 (0.48,0.83)	0.66 (0.50,0.86)
Psychiatric						
Bipolar disease	0.69 (0.49,0.99)	0.70 (0.49,1.00)	0.77 (0.58,1.02)	0.78 (0.59,1.03)	0.75 (0.57,1.00)	0.76 (0.58,1.01)
Depression	1.17 (1.13,1.21)	1.17 (1.12,1.21)	1.15 (1.12,1.19)	1.15 (1.11,1.19)	1.16 (1.12,1.20)	1.15 (1.12,1.19)

	5y Unadjusted odds ratio	Adjusted odds ratio	2y Unadjusted odds ratio	Adjusted odds ratio	1y Unadjusted odds ratio	Adjusted odds ratio
Anxiety	1.14 (1.10,1.20)	1.14 (1.09,1.19)	1.15 (1.10,1.19)	1.14 (1.09,1.18)	1.15 (1.11,1.20)	1.14 (1.10,1.19)
Schizophrenia	0.37 (0.26,0.52)	0.38 (0.28,0.54)	0.38 (0.29,0.51)	0.40 (0.30,0.53)	0.37 (0.28,0.49)	0.39 (0.29,0.51)
Complications due to glucocorticoids						
Osteoporosis	1.11 (1.04,1.19)	1.10 (1.02,1.17)	1.12 (1.06,1.18)	1.10 (1.05,1.16)	1.13 (1.07,1.18)	1.11 (1.06,1.17)
Hip fracture	0.65 (0.55,0.79)	0.66 (0.55,0.79)	0.61 (0.53,0.70)	0.61 (0.54,0.70)	0.61 (0.54,0.69)	0.62 (0.55,0.70)
Wrist fracture	1.01 (0.94,1.08)	1.00 (0.94,1.07)	1.00 (0.95,1.06)	1.00 (0.94,1.05)	1.01 (0.95,1.06)	1.00 (0.94,1.05)
Vertebral fracture	0.73 (0.51,1.06)	0.72 (0.50,1.04)	0.84 (0.64,1.12)	0.84 (0.63,1.11)	0.91 (0.70,1.18)	0.91 (0.70,1.17)
Ophthalmological						
Cataracts	1.10 (1.03,1.16)	1.08 (1.02,1.14)	1.14 (1.09,1.19)	1.12 (1.07,1.17)	1.16 (1.11,1.21)	1.13 (1.08,1.18)
Glaucoma	1.04 (0.97,1.12)	1.03 (0.96,1.10)	1.07 (1.01,1.13)	1.05 (0.99,1.11)	1.08 (1.03,1.14)	1.07 (1.01,1.13)
Infections						
UTI	1.14 (1.10,1.19)	1.12 (1.08,1.17)	1.17 (1.13,1.21)	1.14 (1.11,1.18)	1.16 (1.12,1.20)	1.14 (1.10,1.17)
URTI	1.36 (1.32,1.40)	1.32 (1.29,1.36)	1.40 (1.37,1.44)	1.36 (1.32,1.39)	1.42 (1.38,1.45)	1.37 (1.33,1.41)
LRTI	1.06 (0.97,1.16)	1.06 (0.97,1.15)	1.10 (1.02,1.18)	1.10 (1.02,1.18)	1.11 (1.04,1.19)	1.11 (1.03,1.18)
Skin infections	1.11 (1.05,1.16)	1.10 (1.04,1.15)	1.10 (1.06,1.15)	1.09 (1.04,1.13)	1.11 (1.06,1.15)	1.09 (1.05,1.13)

Abbreviations: Leukaemia, lymphoma (LL), Cardiovascular disease (CVD), Congestive cardiac failure (CCF), Peripheral vascular disease (PVD), Cerebrovascular disease (CVA), Hypertension (HTN), Chronic obstructive pulmonary disease (COPD), Ulcerative colitis (UC), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Osteoarthritis (OA), Type 1 Diabetes mellitus (T1DM), Type 2 Diabetes mellitus (T2DM), Multiple sclerosis (MS), Urinary tract infection (UTI), Upper respiratory tract infection (URTI), Lower respiratory tract infection (LRTI)

Figure 6-1: Likelihood of comorbidities prior to index date expressed as odds Ratios with 95% confidence intervals (unadjusted)

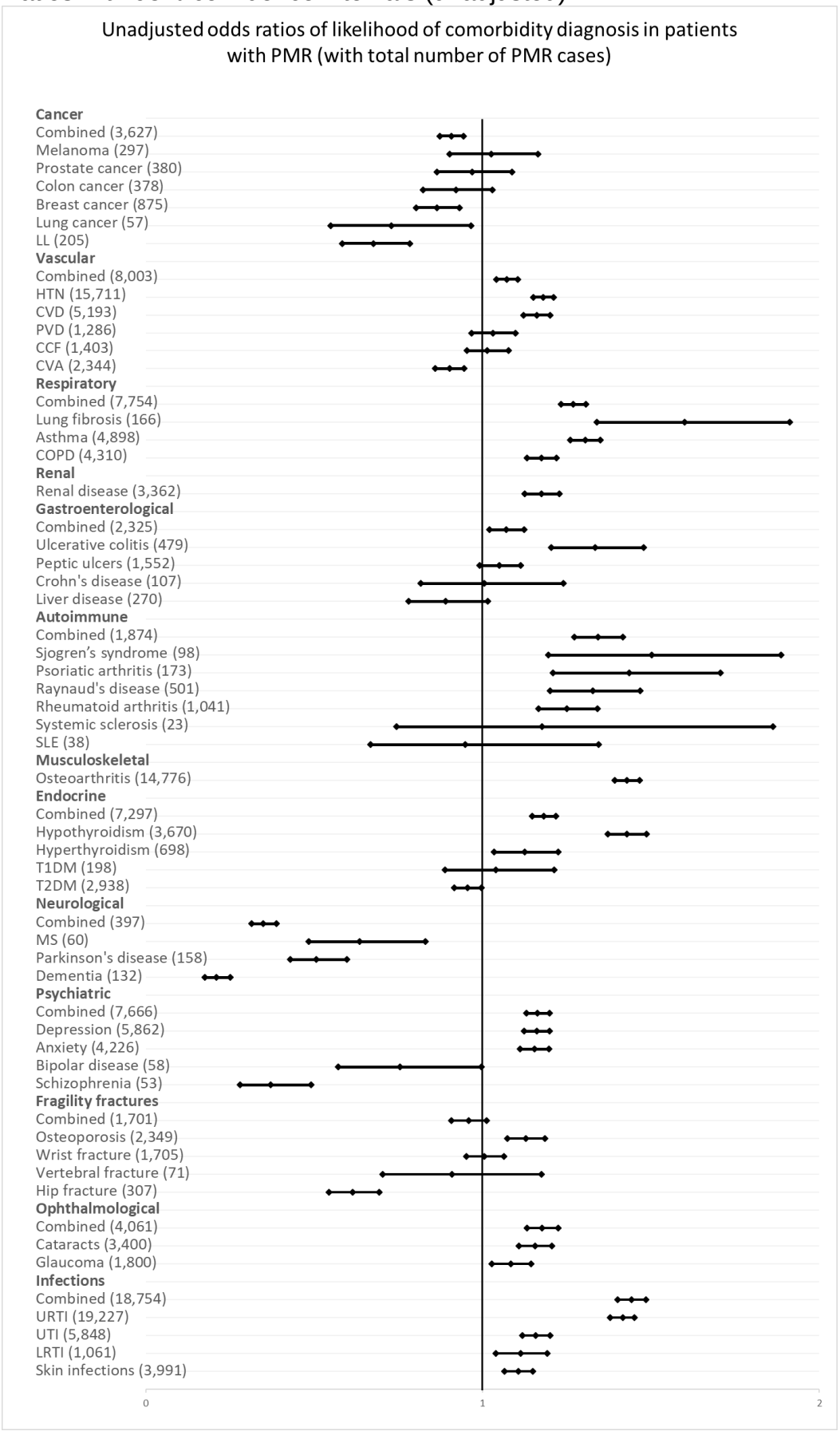
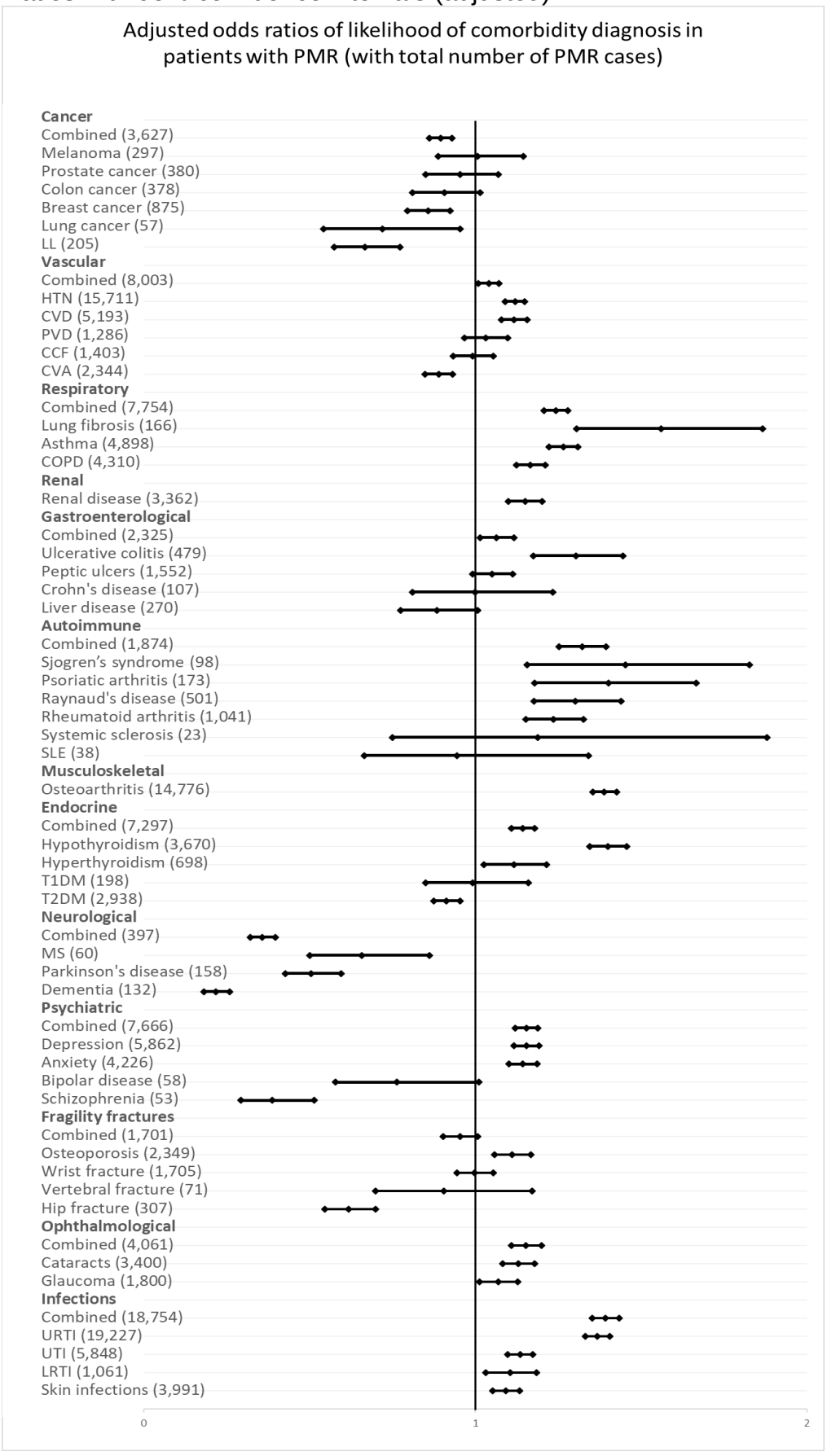


Figure 6-2: Likelihood of comorbidities prior to index date expressed as odds Ratios with 95% confidence intervals (adjusted)



Stratified outcomes

Cancer

Of the six main cancer types, after adjustment for alcohol consumption, BMI category, age, sex and smoking status, three showed no significant difference in diagnosis prior to index date (melanoma, prostate cancer and colon cancer), while in three there was a statistically significant reduction in the likelihood of diagnosis (breast cancer, lung cancer and leukaemia and lymphoma).

Vascular

After adjustment for the previously discussed covariates was applied, two vascular outcomes were significantly more likely in patients with PMR (hypertension and cardiovascular disease), while peripheral vascular disease and congestive cardiac failure did not show a significant difference. Cerebrovascular disease was significantly less likely in patients who had a diagnosis of PMR compared to their matched controls.

Other comorbidities

All of the respiratory outcomes, including lung fibrosis, asthma and COPD were significantly more likely in patients with PMR. Similarly, renal disease and all autoimmune conditions investigated, except systemic sclerosis and SLE were found to be significantly more likely in patients with PMR. In both systemic

sclerosis and SLE the confidence intervals were particularly wide. This was due to the low numbers of patients diagnosed with these conditions (n=23, n=28).

Regarding gastroenterological and endocrine comorbidities, the picture was more mixed. The likelihood of ulcerative colitis, hypothyroidism and hyperthyroidism were significantly increased. However, the likelihood of peptic ulcers, Crohn's disease, liver disease, Addison's disease and type 1 diabetes mellitus were not significantly different between cases and controls. Finally, it was found that type 2 diabetes was significantly less likely in patients who subsequently went on to have a diagnosis of PMR.

All neurological diagnoses tested were statistically significantly less likely in patients with PMR, including multiple sclerosis, Parkinson's disease and dementia. Regarding psychiatric diagnoses, conditions which could be regarded as more severe illnesses, such as schizophrenia, were significantly less likely in patients with PMR. Although the reduction in the likelihood of previous bipolar disease in cases did not reach statistical significance. However, the more common and, usually, less severe psychiatric diagnoses of anxiety and depression, were significantly more likely to have occurred in patients who went on to receive a diagnosis of PMR.

Comorbidities linked to GC prescription

A significant increase in the risk of diagnosis with certain comorbidities, including cataracts, glaucoma and most infectious diseases, was observed in patients with PMR. However, although the likelihood of a diagnosis of osteoporosis being

made was significantly higher in cases compared to controls, the risk of a hip fracture was significantly lower in cases, while wrist and vertebral fractures were not seen to be significantly different in cases or controls.

6.3.3 Cohort study

The total number, proportion, and rate of new, or incident diagnoses with each comorbidity in patients with PMR compared to matched controls, at index date and four time points following this (one, two, five and ten years) are reported in table 6-12. The overall comorbidity burden that cases and controls were subjected to was estimated using the Charlson index score. The number and proportion of patients with each score are then described (table 6-13). Due to small numbers, all those with a Charlson score of greater than 5 were aggregated. Finally, the cumulative probability, with 95% confidence intervals, of each comorbidity is then tabulated (table 6-14). For the Charlson comorbidity index score and cumulative probability, existing diagnoses from prior to index date were included.

Table 6-12: Total number, proportion and rate of incident diagnoses of composite outcomes following index date

	Cases				Controls			
	At risk	**Incident diagnoses**	**%**	**Rate (per 1,000)**	**At risk**	**Incident diagnoses**	**%**	**Rate (per 1,000)**
Cancer	27,990	3,484	12.4	238.1 (230.3,246.1)	129,044	14,645	11.3	238.4 (234.6,242.3)
Vascular	23,340	3,964	17.0	335.8 (325.6,346.5)	112,013	14,080	12.6	266.0 (261.6,270.4)
Respiratory	23,891	1,656	6.9	131.6 (125.4,138.1)	117,916	5,987	5.1	106.2 (103.5,108.9)
Gastroenterological	29,524	743	2.5	47.1 (43.8,50.6)	138,885	2,598	1.9	38.5 (37.1,40.0)
Autoimmune	29,600	1,482	5.0	96.8 (92.0,101.9)	142,414	1,460	1.0	21.2 (20.1,22.3)
Endocrine	24,009	2,640	11.0	213.8 (205.8,222.1)	117,544	8,405	7.2	151.1 (147.9,154.3)
Neurological	31,476	1,877	6.0	112.2 (107.3,117.4)	143,367	8,117	5.7	116.9 (114.4,119.4)
Psychiatric	23,996	1,440	6.0	114.6 (108.8,120.6)	115,832	4,993	4.3	90.2 (87.7,92.8)
Ophthalmological	26,680	3,464	13.0	258.6 (250.1,267.3)	127,763	10,934	8.6	184.3 (180.8,187.8)
Infections	9,382	3,765	40.1	980.7 (949.9,1012.5)	54,009	16,412	30.4	762.6 (751.1,774.4)
Fragility fractures	29,818	1,492	5.0	94.6 (89.9,99.5)	138,582	5,293	3.8	79.5 (77.4,81.7)

Table 6-13: Total number of cases and controls (%) with Charlson index score of composite outcomes following index date

Charlson score	At diagnosis		After one year		Two years		Five years		Ten years	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
0	11,786 (34.7)	61,711 (41.3)	10,277 (30.2)	57,375 (38.4)	9,352 (27.5)	53,873 (36.1)	7,605 (22.4)	46,501 (31.1)	6,533 (19.2)	41,619 (27.9)
1	7,568 (22.3)	32,431 (21.7)	7,219 (21.2)	31,229 (20.9)	6,910 (20.3)	30,178 (20.2)	6,256 (18.4)	27,949 (18.7)	5,615 (16.5)	26,456 (17.7)
2	5,732 (16.9)	25,398 (17.0)	6,014 (17.7)	26,254 (17.6)	6,072 (17.9)	26,775 (17.9)	6,173 (18.2)	27,808 (18.6)	6,136 (18.1)	27,991 (18.7)
3	3,369 (9.9)	14,319 (9.6)	3,843 (11.3)	15,560 (10.4)	4,190 (12.3)	16,669 (11.2)	4,681 (13.8)	18,702 (12.5)	4,951 (14.6)	20,118 (13.5)
4	1,843 (5.4)	7,753 (5.2)	2,306 (6.8)	8,968 (6.0)	2,600 (7.7)	10,031 (6.7)	3,105 (9.1)	12,277 (8.2)	3,530 (10.4)	13,742 (9.2)
5	960 (2.8)	4,016 (2.7)	1,208 (3.6)	4,872 (3.3)	1,404 (4.1)	5,533 (3.7)	1,912 (5.6)	7,196 (4.8)	2,299 (6.8)	8,418 (5.6)
Greater than 5	726 (2.1)	3,808 (2.5)	1,117 (3.3)	5,178 (3.5)	1,456 (4.3)	6,377 (4.3)	2,252 (6.6)	9,003 (6.0)	2,920 (8.6)	11,092 (7.4)

Table 6-14: Cumulative probability of composite outcomes (with 95% confidence intervals) following index date

	At diagnosis		**After one year**		**Two years**		**Five years**		**Ten years**	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Composite outcomes										
Cancer	15.4 (15.0,15.8)	16.4 (16.2,16.6)	17.2 (16.8,17.6)	18.3 (18.1,18.5)	22.7 (22.2,23.2)	23.8 (23.6,24.1)	30.6 (29.9,31.3)	31.8 (31.5,32.1)	40.1 (38.9,41.3)	41.3 (40.7,41.9)
Vascular	30.5 (29.9,31.0)	28.2 (28.0,28.4)	32.7 (32.2,33.2)	30.0 (29.7,30.2)	38.9 (38.4,39.5)	35.1 (34.9,35.4)	47.7 (47.0,48.4)	42.8 (42.5,43.2)	57.5 (56.3,58.6)	51.5 (50.9,52.1)
Respiratory	27.5 (27.0,28.0)	23.2 (23.0,23.4)	28.5 (28.0,29.0)	24.0 (23.8,24.3)	31.1 (30.5,31.6)	26.4 (26.1,26.6)	34.8 (34.2,35.4)	29.6 (29.3,29.8)	39.5 (38.5,40.5)	33.2 (32.7,33.7)
Gastroenterological	8.6 (8.3,8.9)	7.9 (7.8,8.1)	9.0 (8.7,9.3)	8.3 (8.1,8.4)	10.2 (9.9,10.6)	9.3 (9.2,9.5)	12.1 (11.7,12.5)	10.9 (10.7,11.1)	14.5 (13.7,15.2)	12.6 (12.2,12.9)
Autoimmune	9.6 (9.2,9.9)	5.2 (5.1,5.4)	10.6 (10.3,11.0)	5.4 (5.3,5.6)	12.6 (12.2,13.0)	6.0 (5.9,6.2)	15.0 (14.5,15.5)	7.0 (6.8,7.1)	17.4 (16.7,18.2)	7.9 (7.7,8.2)
Endocrine	28.2 (27.7,28.7)	23.8 (23.5,24.0)	29.7 (29.2,30.2)	24.9 (24.6,25.1)	33.6 (33.1,34.2)	28.1 (27.8,28.3)	38.9 (38.3,39.6)	33.0 (32.7,33.3)	45.0 (43.9,46.1)	38.0 (37.5,38.5)
Neurological	2.5 (2.3,2.6)	5.3 (5.2,5.4)	3.3 (3.1,3.5)	6.2 (6.0,6.3)	6.2 (5.9,6.5)	9.2 (9.0,9.3)	12.3 (11.8,12.9)	14.6 (14.4,14.9)	21.2 (20.1,22.5)	23.4 (22.8,24.0)
Psychiatric	27.0 (26.5,27.5)	24.5 (24.3,24.8)	27.9 (27.4,28.4)	25.2 (25.0,25.5)	30.3 (29.8,30.8)	27.2 (26.9,27.4)	33.5 (32.9,34.1)	29.8 (29.5,30.1)	36.9 (36.0,37.9)	32.9 (32.5,33.4)
Ophthalmological	19.5 (19.1,20.0)	16.8 (16.6,17.0)	21.9 (21.4,22.4)	18.3 (18.1,18.5)	27.6 (27.1,28.1)	22.6 (22.4,22.9)	34.8 (34.2,35.5)	29.2 (28.9,29.5)	43.8 (42.6,45.0)	36.5 (35.9,37.1)
Infections	74.5 (74.0,75.0)	68.0 (67.7,68.2)	77.0 (76.6,77.5)	70.4 (70.1,70.6)	82.6 (82.1,83.0)	76.1 (75.9,76.4)	88.3 (87.9,88.8)	82.6 (82.3,82.8)	92.2 (91.5,92.8)	88.0 (87.6,88.4)
Fragility fracture	7.9 (7.6,8.3)	8.4 (8.2,8.5)	8.7 (8.4,9.0)	9.0 (8.9,9.2)	10.9 (10.5,11.3)	11.1 (10.9,11.2)	15.5 (14.9,16.0)	14.6 (14.4,14.9)	21.8 (20.7,22.9)	20.2 (19.7,20.7)

Charlson Index

The overall burden of comorbidities among patients with PMR and matched controls following index date, was measured using the Charlson comorbidity index. At the time of diagnosis as well as the four succeeding time points, the burden of disease was higher in cases compared to controls. The proportion of patients with PMR with a Charlson score of zero was lower at every measured point for cases compared to controls. The difference in the two proportions increased from 6.6% at time of diagnosis to 8.7% at ten years. Furthermore, the proportion of cases with a score of 1-5 was higher at diagnosis, as well as at one and two years after. However, similar to the case control study, the proportion of controls with a Charlson score of greater than 5 was higher. At every time point after diagnosis, the average Charlson comorbidity score was higher in cases compared to controls.

Composite Outcomes

In all but three of the combined outcomes the cumulative probability of a comorbidity being present either at index date, or developing one, two, five or ten years following it, was higher in patients with PMR compared to their matched controls. The composite outcomes with an increase in the cumulative probability of diagnosis were vascular, respiratory, gastroenterological, autoimmune, endocrine, psychiatric, and ophthalmological diseases. However, in two composite outcomes the converse was found. The proportion of patients who had an existing diagnosis of PMR and went on to develop any cancer or neurological

disease was lower compared to controls. This difference also persisted at each time point.

Finally, in the case of fragility fractures, the picture was more mixed. Here, at the first three time points, at diagnosis and one and two years subsequently, the cumulative probability of a fragility fracture was higher in controls compared to cases (by 0.5%, 0.3% and 0.2% respectively). However, after five and ten years of follow up, the probability was higher in cases and the difference was increasing (0.9% and 1.6%).

The total number, proportion and rate of diagnosis with stratified comorbidities are shown in table 6-15. Again, this table also illustrates the total number of patients who entered each analysis per comorbidity, after patients who had a pre-existing diagnosis were excluded. The cumulative probability of a diagnosis with each comorbidity is then summarised in table 6-16.

Table 6-15: Total number of patients included in cohort study, total and rate of stratified comorbidity diagnosis

	Cases At risk	New diagnoses	%	Rate (per 1,000)	Controls At risk	New diagnoses	%	Rate (per 1,000)
Cancer								
Breast cancer	31,063	380	1.2	22.7 (20.5,25.1)	144,350	1,811	1.3	25.9 (24.7,27.1)
Prostate cancer	31,508	402	1.3	23.7 (21.5,26.1)	147,408	1,457	1.0	20.3 (19.3,21.4)
Lung cancer	31,915	425	1.3	24.6 (22.4,27.1)	148,869	2,087	1.4	28.8 (27.6,30.0)
Colon cancer	31,569	409	1.3	24.0 (21.8,26.5)	147,294	1,759	1.2	24.6 (23.4,25.7)
Melanoma	31,673	142	0.4	8.3 (7.0,9.8)	147,993	605	0.4	8.4 (7.8,9.1)
Leukaemia, lymphoma	31,738	378	1.2	22.1 (20.0,24.4)	147,838	1386	0.9	19.3 (18.3,20.3)
Vascular								
CVD	26,523	1,803	6.8	128.8 (122.9,134.8)	127,222	5,,966	4.7	97.3 (94.9,99.8)
CCF	30,353	1,844	6.1	114.2 (109.1,119.5)	142,253	6,041	4.2	87.7 (85.5,89.9)
PVD	30,529	1,117	3.7	68.6 (64.7,72.8)	143,157	3,241	2.3	46.7 (45.1,48.3)
CVA	29,327	2,076	7.1	134.0 (128.3,139.8)	136,414	7,936	5.8	120.9 (118.3,123.6)
HTN	15,416	3,269	21.2	445.1 (430.1,460.7)	78,654	12,646	16.1	366.2 (359.8,372.6)
Respiratory								
Asthma	26,920	772	2.9	53.4 (49.8,57.3)	130,438	2,735	2.1	43.3 (41.8,45.0)
COPD	27,405	1,337	4.9	92.1 (87.3,97.2)	130,887	4,787	3.7	76.2 (74.1,78.4)
Lung fibrosis	31,784	234	0.7	13.6 (12.0,15.5)	148,859	629	0.4	8.7 (8.0,9.4)
Renal								
Renal disease	27,755	5,167	18.6	377.0 (366.8,387.4)	132,747	16,517	12.4	270.1 (266.0,274.2)
Gastroenterological								
Moderate liver disease	31,667	214	0.7	12.5 (10.9,14.3)	147,865	823	0.6	11.4 (10.7,12.2)
Peptic ulcers	30,364	360	1.2	22.1 (19.9,24.5)	142,400	1,349	0.9	19.5 (18.5,20.6)
Crohn's disease	31,873	28	0.1	1.6 (1.1,2.3)	148,907	78	0.1	1.1 (0.9,1.3)
Ulcerative colitis	31,476	184	0.6	10.8 (9.4,12.5)	147,656	455	0.3	6.3 (5.8,6.9)
Autoimmune and musculoskeletal								
SLE	31,940	36	0.1	2.1 (1.5,2.9)	149,237	35	0.0	0.5 (0.3,0.7)
Systemic sclerosis	31,959	16	0.1	0.9 (0.6,1.5)	149,338	30	0.0	0.4 (0.3,0.6)
Rheumatoid arthritis	30,562	1,079	3.5	67.4 (63.5,71.6)	145,335	701	0.5	9.9 (9.2,10.7)
Sjogren’s syndrome	31,875	54	0.2	3.1 (2.4,4.1)	149,110	78	0.1	1.1 (0.9,1.3)
Psoriatic arthritis	31,766	190	0.6	11.1 (9.6,12.8)	148,840	102	0.1	1.4 (1.2,1.7)
Raynaud's disease	31,431	222	0.7	13.1 (11.5,14.9)	147,507	634	0.4	8.8 (8.2,9.6)
Osteoarthritis	14,481	3,646	25.2	566.5 (548.4,585.2)	89,580	11,684	13.0	293.4 (288.1,298.8)

	Cases At risk	New diagnoses	%	Rate (per 1,000)	Controls At risk	New diagnoses	%	Rate (per 1,000)
Endocrine								
Hyperthyroidism	31,240	201	0.6	11.9 (10.4,13.7)	146,381	605	0.4	8.5 (7.8,9.2)
Hypothyroidism	27,978	977	3.5	65.6 (61.6,69.9)	136,028	3,454	2.5	52.7 (51.0,54.5)
T1DM	31,774	53	0.2	3.1 (2.4,4.0)	148,485	147	0.1	2.0 (1.7,2.4)
T2DM	28,646	1,998	7.0	132.6 (126.9,138.5)	134,003	5,688	4.2	88.3 (86.0,90.6)
Addison's disease	31,963	32	0.1	1.8 (1.3,2.6)	149,362	34	0.0	0.5 (0.3,0.7)
Neurological and psychiatric								
Dementia	31,770	1,687	5.3	99.6 (95.0,104.5)	145,852	7,439	5.1	105.4 (103.0,107.8)
Parkinson's disease	31,796	260	0.8	15.1 (13.4,17.1)	147,810	1,013	0.7	14.1 (13.2,15.0)
MS	31,923	7	0.0	0.4 (0.2,0.8)	148,971	26	0.0	0.4 (0.2,0.5)
Psychiatric								
Bipolar disease	31,926	18	0.1	1.0 (0.7,1.7)	149,064	66	0.0	0.9 (0.7,1.2)
Depression	25,855	1,167	4.5	85.5 (80.8,90.6)	123,888	3,683	3.0	61.7 (59.7,63.7)
Anxiety	27,551	966	3.5	65.9 (61.8,70.2)	130,889	3,504	2.7	55.8 (54.0,57.7)
Schizophrenia	31,928	19	0.1	1.1 (0.7,1.7)	148,760	84	0.1	1.2 (0.9,1.4)
Complications due to glucocorticoids								
Osteoporosis	29,212	3,420	11.7	236.2 (228.4,244.3)	138,296	7,336	5.3	111.5 (108.9,114.0)
Hip fracture	31,614	918	2.9	54.2 (50.8,57.8)	146,819	3,480	2.4	48.9 (47.3,50.6)
Wrist fracture	30,184	574	1.9	35.5 (32.7,38.5)	141,118	2,114	1.5	31.0 (29.7,32.4)
Vertebral fracture	31,903	210	0.7	12.2 (10.6,13.9)	149,015	424	0.3	5.8 (5.3,6.4)
Ophthalmological								
Cataracts	28,141	3,121	11.1	217.9 (210.4,225.7)	133,985	9,658	7.2	154.0 (150.9,157.1)
Glaucoma	30,038	898	3.0	56.2 (52.7,60.0)	141,196	2,998	2.1	44.1 (42.5,45.7)
Infections								
UTI	25,585	3,121	12.2	242.1 (233.7,250.7)	122,860	10,995	8.9	192.2 (188.7,195.9)
URTI	11,806	3,472	29.4	665.3 (643.6,687.8)	66,482	14,659	22.0	527.1 (518.7,535.8)
LRTI	30,801	1,503	4.9	91.1 (86.6,95.8)	144,614	5,174	3.6	73.8 (71.8,75.8)
Skin infections	27,560	3,242	11.8	230.7 (222.9,238.8)	130,571	10,359	7.9	168.7 (165.5,172.0)

Abbreviations: Leukaemia, lymphoma (LL), Cardiovascular disease (CVD), Congestive cardiac failure (CCF), Peripheral vascular disease (PVD), Cerebrovascular disease (CVA), Hypertension (HTN), Chronic obstructive pulmonary disease (COPD), Ulcerative colitis (UC), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Osteoarthritis (OA), Type 1 Diabetes mellitus (T1DM), Type 2 Diabetes mellitus (T2DM), Multiple sclerosis (MS), Urinary tract infection (UTI), Upper respiratory tract infection (URTI), Lower respiratory tract infection (LRTI)

Table 6-16: Cumulative probability of stratified outcomes (with 95% confidence intervals) following index date

	At diagnosis		After one year		Two years		Five years		Ten years	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Cancer										
Breast cancer	3.2 (3.0,3.4)	3.9 (3.8,4.0)	3.4 (3.2,3.6)	4.1 (4.0,4.2)	4.1 (3.9,4.3)	4.9 (4.8,5.0)	5.2 (4.9,5.5)	6.0 (5.8,6.1)	6.6 (6.1,7.2)	7.5 (7.2,7.8)
Prostate cancer	2.0 (1.8,2.2)	1.7 (1.6,1.7)	2.2 (2.0,2.4)	1.9 (1.8,1.9)	2.8 (2.6,3.0)	2.4 (2.3,2.5)	3.6 (3.4,3.9)	3.3 (3.2,3.5)	4.7 (4.2,5.2)	4.6 (4.3,4.8)
Lung cancer	0.6 (0.5,0.7)	0.7 (0.7,0.7)	0.9 (0.8,1.0)	1.0 (1.0,1.1)	1.5 (1.3,1.6)	1.9 (1.8,1.9)	2.5 (2.2,2.7)	3.0 (2.9,3.2)	3.6 (3.2,4.2)	4.5 (4.2,4.8)
Colon cancer	1.6 (1.5,1.7)	1.8 (1.7,1.8)	1.8 (1.7,2.0)	2.0 (1.9,2.1)	2.5 (2.4,2.7)	2.7 (2.6,2.8)	3.6 (3.3,3.9)	3.9 (3.7,4.0)	5.2 (4.6,5.8)	5.2 (5.0,5.5)
Melanoma	1.1 (1.0,1.2)	1.1 (1.1,1.2)	1.2 (1.1,1.4)	1.2 (1.1,1.3)	1.5 (1.3,1.6)	1.5 (1.4,1.5)	1.8 (1.6,2.0)	1.8 (1.7,1.9)	2.1 (1.9,2.5)	2.4 (2.2,2.5)
LL	1.2 (1.1,1.3)	1.3 (1.3,1.4)	1.4 (1.2,1.5)	1.5 (1.4,1.6)	2.0 (1.8,2.1)	2.1 (2.0,2.2)	2.7 (2.5,3.0)	3.0 (2.9,3.1)	4.0 (3.5,4.5)	4.0 (3.7,4.2)
Vascular										
CVD	18.9 (18.5,19.4)	16.6 (16.4,16.8)	20.0 (19.6,20.5)	17.4 (17.2,17.6)	23.1 (22.6,23.6)	19.8 (19.5,20.0)	27.2 (26.6,27.8)	23.1 (22.8,23.4)	32.5 (31.4,33.5)	27.5 (27.0,28.0)
CCF	6.6 (6.3,6.8)	5.9 (5.8,6.1)	7.6 (7.3,7.9)	6.7 (6.6,6.8)	10.5 (10.1,10.8)	9.0 (8.9,9.2)	15.1 (14.6,15.7)	12.7 (12.5,13.0)	20.9 (19.8,21.9)	17.8 (17.3,18.3)
PVD	5.5 (5.3,5.8)	5.0 (4.9,5.1)	6.2 (5.9,6.5)	5.4 (5.3,5.5)	7.9 (7.5,8.2)	6.7 (6.6,6.8)	10.9 (10.4,11.4)	8.7 (8.5,8.9)	14.5 (13.7,15.4)	10.6 (10.3,11.0)
CVA	9.9 (9.6,10.2)	10.3 (10.2,10.5)	10.9 (10.6,11.3)	11.3 (11.2,11.5)	14.4 (14.0,14.8)	14.4 (14.2,14.6)	19.8 (19.2,20.4)	19.3 (19.0,19.6)	27.0 (25.9,28.1)	25.3 (24.7,25.8)
HTN	55.4 (54.9,56.0)	51.0 (50.7,51.2)	57.6 (57.1,58.2)	52.8 (52.5,53.0)	62.6 (62.0,63.1)	57.6 (57.4,57.9)	68.9 (68.2,69.5)	63.8 (63.4,64.1)	74.2 (73.2,75.1)	69.8 (69.3,70.3)
Respiratory										
Asthma	17.0 (16.6,17.5)	14.0 (13.8,14.2)	17.5 (17.1,17.9)	14.4 (14.2,14.6)	18.9 (18.5,19.4)	15.5 (15.3,15.7)	20.6 (20.1,21.1)	16.8 (16.6,17.1)	23.1 (22.3,23.9)	18.4 (18.0,18.7)

	At diagnosis		After one year		Two years		Five years		Ten years	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
COPD	16.0 (15.6,16.4)	14.0 (13.8,14.1)	16.8 (16.4,17.2)	14.7 (14.5,14.8)	18.9 (18.4,19.4)	16.5 (16.3,16.7)	22.1 (21.5,22.6)	19.1 (18.9,19.4)	25.3 (24.5,26.2)	22.1 (21.7,22.5)
Lung fibrosis	0.9 (0.8,1.0)	0.5 (0.5,0.5)	1.0 (0.9,1.1)	0.6 (0.5,0.6)	1.3 (1.2,1.4)	0.8 (0.8,0.9)	1.9 (1.7,2.2)	1.3 (1.2,1.4)	2.7 (2.3,3.1)	1.7 (1.5,1.8)
Renal										
Renal disease	16.9 (16.5,17.4)	14.0 (13.8,14.2)	20.1 (19.6,20.5)	16.1 (15.9,16.3)	28.3 (27.8,28.9)	22.6 (22.4,22.9)	39.8 (39.0,40.5)	32.1 (31.7,32.4)	52.3 (51.1,53.6)	42.7 (42.0,43.3)
Gastroenterological										
Liver disease	1.2 (1.1,1.3)	1.2 (1.2,1.3)	1.3 (1.2,1.4)	1.3 (1.3,1.4)	1.7 (1.5,1.9)	1.7 (1.6,1.8)	2.2 (2.0,2.4)	2.2 (2.1,2.3)	2.9 (2.5,3.4)	2.7 (2.6,2.9)
Peptic ulcers	5.6 (5.3,5.9)	5.2 (5.1,5.4)	5.8 (5.5,6.0)	5.4 (5.3,5.6)	6.4 (6.1,6.7)	6.0 (5.8,6.1)	7.3 (7.0,7.7)	6.8 (6.6,6.9)	8.6 (8.0,9.1)	7.8 (7.5,8.1)
Crohn's disease	0.4 (0.3,0.5)	0.4 (0.4,0.4)	0.4 (0.3,0.5)	0.4 (0.4,0.4)	0.5 (0.4,0.5)	0.4 (0.4,0.5)	0.5 (0.4,0.6)	0.5 (0.4,0.5)	0.6 (0.5,0.8)	0.5 (0.5,0.6)
UC	1.8 (1.7,2.0)	1.3 (1.3,1.4)	2.0 (1.8,2.1)	1.4 (1.4,1.5)	2.2 (2.1,2.4)	1.6 (1.5,1.7)	2.6 (2.4,2.9)	1.9 (1.8,2.0)	3.1 (2.8,3.5)	2.1 (2.0,2.3)
Autoimmune and musculoskeletal										
SLE	0.2 (0.1,0.2)	0.2 (0.1,0.2)	0.2 (0.2,0.3)	0.2 (0.1,0.2)	0.3 (0.2,0.3)	0.2 (0.2,0.2)	0.3 (0.3,0.4)	0.2 (0.2,0.2)	0.4 (0.3,0.5)	0.2 (0.2,0.2)
Systemic sclerosis	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.2)	0.1 (0.1,0.1)	0.2 (0.1,0.2)	0.1 (0.1,0.1)	0.3 (0.1,0.4)	0.2 (0.1,0.2)
RA	6.1 (5.8,6.4)	3.0 (3.0,3.1)	6.8 (6.5,7.1)	3.1 (3.1,3.2)	8.2 (7.9,8.5)	3.5 (3.4,3.6)	9.7 (9.3,10.1)	3.9 (3.7,4.0)	11.5 (10.9,12.2)	4.3 (4.1,4.5)
Sjogren’s syndrome	0.4 (0.3,0.5)	0.3 (0.2,0.3)	0.4 (0.4,0.5)	0.3 (0.2,0.3)	0.6 (0.5,0.6)	0.3 (0.3,0.3)	0.6 (0.5,0.7)	0.3 (0.3,0.4)	0.8 (0.6,1.1)	0.4 (0.3,0.4)
Psoriatic arthritis	0.9 (0.8,1.0)	0.5 (0.4,0.5)	1.1 (0.9,1.2)	0.5 (0.4,0.5)	1.3 (1.2,1.5)	0.5 (0.5,0.5)	1.7 (1.5,1.9)	0.6 (0.5,0.6)	2.0 (1.7,2.3)	0.6 (0.6,0.7)
Raynaud's disease	1.9 (1.8,2.1)	1.5 (1.4,1.5)	2.1 (1.9,2.2)	1.6 (1.5,1.6)	2.4 (2.3,2.6)	1.8 (1.7,1.9)	3.1 (2.9,3.4)	2.2 (2.1,2.3)	3.7 (3.3,4.1)	2.7 (2.5,2.9)

	At diagnosis		After one year		Two years		Five years		Ten years	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
OA	58.6 (58.0,59.1)	43.5 (43.2,43.8)	61.4 (60.9,62.0)	45.2 (44.9,45.4)	67.3 (66.7,67.8)	49.7 (49.4,50.0)	73.3 (72.7,73.9)	55.7 (55.4,56.1)	78.6 (77.6,79.5)	61.3 (60.8,61.9)
Endocrine										
Hyperthyroidism	2.6 (2.4,2.8)	2.3 (2.2,2.4)	2.7 (2.5,2.9)	2.4 (2.3,2.5)	3.1 (2.9,3.3)	2.6 (2.5,2.7)	3.6 (3.3,3.8)	3.0 (2.9,3.1)	4.0 (3.6,4.4)	3.5 (3.3,3.6)
Hypothyroidism	13.8 (13.4,14.2)	10.1 (9.9,10.2)	14.3 (13.9,14.7)	10.5 (10.4,10.7)	15.9 (15.5,16.4)	11.9 (11.7,12.1)	18.4 (17.9,18.9)	14.1 (13.8,14.3)	21.4 (20.6,22.3)	16.4 (16.0,16.8)
T1DM	0.8 (0.7,0.9)	0.7 (0.7,0.8)	0.8 (0.7,0.9)	0.7 (0.7,0.8)	0.9 (0.8,1.0)	0.8 (0.7,0.8)	1.0 (0.8,1.1)	0.9 (0.8,0.9)	1.0 (0.9,1.2)	0.9 (0.9,1.0)
T2DM	12.9 (12.6,13.3)	11.8 (11.7,12.0)	14.1 (13.7,14.4)	12.6 (12.4,12.7)	16.9 (16.5,17.4)	14.8 (14.6,15.0)	20.8 (20.2,21.4)	18.2 (18.0,18.5)	25.3 (24.4,26.3)	21.9 (21.4,22.3)
Addison's disease	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.2)	0.1 (0.1,0.1)	0.2 (0.1,0.2)	0.1 (0.1,0.1)	0.3 (0.2,0.4)	0.1 (0.1,0.1)	0.3 (0.2,0.4)	0.1 (0.1,0.2)
Neurological										
Dementia	1.4 (1.2,1.5)	3.4 (3.3,3.5)	2.0 (1.9,2.2)	4.2 (4.1,4.3)	4.6 (4.4,4.9)	7.0 (6.8,7.1)	10.3 (9.8,10.9)	12.1 (11.8,12.4)	19.1 (18.0,20.4)	20.5 (19.9,21.1)
Parkinson's disease	0.8 (0.7,0.9)	1.3 (1.2,1.4)	0.9 (0.8,1.0)	1.4 (1.4,1.5)	1.4 (1.3,1.5)	1.8 (1.8,1.9)	2.0 (1.8,2.3)	2.5 (2.4,2.6)	2.9 (2.5,3.4)	3.3 (3.1,3.5)
MS	0.2 (0.2,0.3)	0.3 (0.3,0.4)	0.2 (0.2,0.3)	0.4 (0.3,0.4)	0.2 (0.2,0.3)	0.4 (0.3,0.4)	0.2 (0.2,0.3)	0.4 (0.3,0.4)	0.3 (0.2,0.4)	0.4 (0.3,0.4)
Psychiatric										
Schizophrenia	0.2 (0.2,0.2)	0.5 (0.5,0.5)	0.2 (0.2,0.3)	0.5 (0.5,0.6)	0.2 (0.2,0.3)	0.6 (0.5,0.6)	0.3 (0.2,0.4)	0.6 (0.5,0.6)	0.4 (0.3,0.6)	0.6 (0.6,0.7)
Bipolar disease	0.2 (0.2,0.3)	0.3 (0.3,0.3)	0.2 (0.2,0.3)	0.3 (0.3,0.3)	0.2 (0.2,0.3)	0.3 (0.3,0.4)	0.3 (0.2,0.4)	0.4 (0.3,0.4)	0.3 (0.2,0.4)	0.4 (0.3,0.5)
Depression	20.8 (20.4,21.3)	18.7 (18.5,18.9)	21.6 (21.2,22.1)	19.2 (19.0,19.5)	23.6 (23.1,24.1)	20.7 (20.5,20.9)	26.1 (25.6,26.7)	22.6 (22.4,22.9)	28.8 (27.9,29.6)	24.7 (24.3,25.0)
Anxiety	15.1 (14.7,15.5)	13.8 (13.6,14.0)	15.6 (15.2,16.0)	14.2 (14.1,14.4)	17.3 (16.9,17.8)	15.6 (15.4,15.8)	19.8 (19.3,20.4)	17.6 (17.3,17.8)	22.7 (21.9,23.6)	20.2 (19.8,20.6)

	At diagnosis		After one year		Two years		Five years		Ten years	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Osteoporotic										
Osteoporosis	12.6 (12.3,13.0)	8.8 (8.7,9.0)	15.0 (14.6,15.4)	9.7 (9.6,9.9)	19.6 (19.1,20.1)	12.6 (12.4,12.8)	25.7 (25.1,26.4)	17.4 (17.1,17.7)	32.9 (31.7,34.1)	24.3 (23.7,24.8)
Hip fracture	1.7 (1.5,1.8)	2.3 (2.2,2.3)	2.1 (1.9,2.3)	2.7 (2.6,2.8)	3.4 (3.2,3.7)	4.0 (3.9,4.1)	6.3 (6.0,6.8)	6.5 (6.3,6.7)	11.4 (10.5,12.4)	10.6 (10.1,11.0)
Wrist fracture	6.3 (6.0,6.6)	6.2 (6.1,6.3)	6.6 (6.3,6.9)	6.5 (6.3,6.6)	7.4 (7.1,7.8)	7.4 (7.2,7.5)	9.2 (8.8,9.6)	8.7 (8.5,8.9)	11.3 (10.6,12.0)	10.8 (10.5,11.2)
Vertebral fracture	0.4 (0.3,0.5)	0.4 (0.3,0.4)	0.5 (0.4,0.6)	0.4 (0.4,0.4)	0.9 (0.8,1.0)	0.5 (0.5,0.6)	1.4 (1.2,1.6)	0.9 (0.8,0.9)	2.2 (1.9,2.7)	1.6 (1.4,1.8)
Ophthalmological										
Cataracts	14.5 (14.1,14.9)	12.3 (12.1,12.4)	16.6 (16.2,17.0)	13.6 (13.4,13.7)	21.7 (21.2,22.2)	17.4 (17.2,17.6)	28.6 (28.0,29.3)	23.3 (23.0,23.6)	37.4 (36.2,38.7)	30.1 (29.6,30.7)
Glaucoma	7.0 (6.7,7.3)	6.3 (6.2,6.4)	7.6 (7.4,8.0)	6.7 (6.6,6.8)	9.2 (8.8,9.5)	7.9 (7.7,8.0)	11.1 (10.7,11.6)	9.9 (9.7,10.1)	13.4 (12.7,14.1)	12.1 (11.7,12.5)
Infections										
UTI	22.8 (22.3,23.3)	20.3 (20.0,20.5)	24.6 (24.1,25.1)	21.7 (21.5,21.9)	29.4 (28.8,29.9)	25.9 (25.7,26.2)	37.2 (36.5,37.9)	32.5 (32.2,32.8)	46.9 (45.7,48.2)	40.6 (40.0,41.2)
URTI	66.9 (66.4,67.5)	59.6 (59.3,59.8)	69.2 (68.7,69.7)	61.7 (61.5,62.0)	74.5 (74.0,75.0)	67.1 (66.8,67.3)	80.3 (79.7,80.8)	73.3 (73.0,73.6)	85.0 (84.2,85.8)	79.3 (78.8,79.7)
LRTI	4.7 (4.5,4.9)	4.1 (4.0,4.2)	5.4 (5.1,5.6)	4.7 (4.6,4.8)	7.6 (7.3,8.0)	6.7 (6.6,6.9)	12.2 (11.7,12.7)	10.1 (9.8,10.3)	18.8 (17.8,19.9)	15.2 (14.7,15.7)
Skin infections	16.4 (16.0,16.9)	14.7 (14.6,14.9)	18.5 (18.1,18.9)	16.1 (15.9,16.3)	23.5 (23.0,24.0)	20.1 (19.8,20.3)	31.3 (30.7,32.0)	26.4 (26.1,26.7)	40.3 (39.1,41.6)	34.4 (33.8,35.0)

Abbreviations: Leukaemia, lymphoma (LL), Cardiovascular disease (CVD), Congestive cardiac failure (CCF), Peripheral vascular disease (PVD), Cerebrovascular disease (CVA), Hypertension (HTN), Chronic obstructive pulmonary disease (COPD), Ulcerative colitis (UC), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Osteoarthritis (OA), Type 1 Diabetes mellitus (T1DM), Type 2 Diabetes mellitus (T2DM), Multiple sclerosis (MS), Urinary tract infection (UTI), Upper respiratory tract infection (URTI), Lower respiratory tract infection (LRTI)

Stratified outcomes

Cancer

Cancer diagnoses were stratified into six major cancer types, breast, prostate, lung, colorectal, leukaemia and lymphoma and melanoma. The cumulative probability of the majority of the individual cancer types was higher in the control group compared to patients with PMR. This was true at every time point in the case of breast, lung and colon cancer as well as leukaemia and lymphoma. In the case of prostate cancer, however, the cumulative probability of developing this was higher in cases rather than controls. Finally, the picture was mixed with melanoma as the cumulative probability was higher at times during follow up for either cases or controls.

Vascular

Following index date, the cumulative probability of most of the stratified vascular comorbidities, including cardiovascular disease, congestive cardiac failure, peripheral vascular disease and hypertension was consistently higher in patients with PMR when compared to those without. In each of these cases, the difference between cases and controls increased over the ten year follow up period. In the case of cerebrovascular disease, at the time of diagnosis and at one year of follow up the probability of developing this comorbidity was higher in controls rather than cases. However, after two years of follow up, the probability of cerebrovascular disease became higher in cases, similar to the other vascular comorbidities, although the difference was much less.

Other comorbidities

All the stratified respiratory, autoimmune, endocrine, ophthalmological and infection related comorbidities exhibited an increased cumulative probability of diagnosis in people with PMR, and this was maintained over time. These comorbidities included asthma, COPD, lung fibrosis, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, Psoriatic arthritis, Raynaud's disease, osteoarthritis, hyper- and hypothyroid disease, type 1 and type 2 diabetes mellitus, Addison's disease, cataracts, glaucoma as well as urinary tract, upper and lower respiratory tract and skin infections.

All of the comorbidities within the gastroenterological and osteoporosis categories showed a sustained increase in the cumulative probability of diagnosis in patients with PMR, with the exception of liver disease and hip fractures. Liver disease had a very similar cumulative probability in both cases and controls, but was slightly higher in controls in the first five years following index date, and cases at ten years following index date. All other osteoporotic linked outcomes were higher in patients with a pre-existing diagnosis of PMR except hip fracture. In this case, similar to liver disease, the cumulative probability of this comorbidity was higher in the control group until ten years following index date, at which time it was higher in patients with PMR.

Overall

A number of chronic and acute conditions developed particularly high cumulative probabilities over the ten year follow up period in this study. For example, chronic conditions such as hypertension and osteoarthritis affected greater than half of

the patients across most of the study period. Furthermore, greater than 88% of patients in the study had received a code denoting that they had developed an infectious disease at ten years of follow up; with upper respiratory tract infections being particularly common.

Of the other composite outcomes, more than 50% of patients had experienced a vascular event, and more than 40% had received a diagnosis of a cancer or developed a degree of renal disease. Psychiatric, respiratory, endocrine and osteoporosis related conditions affected more than 30% of patients.

In order to ascertain whether these differences in cumulative probability of comorbidities in patients with PMR and their matched controls was significantly different, Cox proportional hazards regression was employed to calculate hazard ratios with 95% confidence intervals (both crude and adjusted for BMI category, age, sex, smoking status and alcohol consumption). However, prior to presenting these results, the data was tested to ensure that the Cox proportional hazard model criteria were not violated.

Statistical testing of Cox proportional hazards

As discussed in chapter 6.2.7, in order to ascertain whether the Cox proportional hazards model is an appropriate model, testing was performed to ensure that the proportional hazards requirement following index date was met. In order to do this, Kaplan-Meier survival estimates were produced to graphically assess whether the hazards altered between the covariates of interest. The Kaplan-Meier charts are enclosed as appendix 6.

Reassuringly, for all the comorbid outcomes tested, the proportional hazards assumption was then met. Many of the comorbidities tested showed little difference in the rate of diagnosis between cases and controls, with survival curves often being very similar. Of the comorbidities in which differences in survival were seen, the hazards were proportional. Satisfied that the requirements of the model were met, the hazard ratios can be reported.

Composite outcomes

The results for the composite outcomes are summarised in table 6-17.

Table 6-17: Hazard ratios (including 95% confidence intervals) illustrating likelihood of combined comorbidity following index date

	Hazard ratio (unadjusted)	**Hazard ratio (adjusted)**
Cancer	1.00 (0.96,1.03)	0.98 (0.94,1.01)
Vascular	1.26 (1.22,1.31)	1.23 (1.19,1.28)
Respiratory	1.25 (1.18,1.31)	1.25 (1.18,1.32)
Gastroenterological	1.22 (1.13,1.33)	1.21 (1.12,1.32)
Autoimmune	4.62 (4.29,4.97)	4.68 (4.35,5.03)
Endocrine	1.42 (1.36,1.48)	1.41 (1.35,1.47)
Neurological	0.95 (0.90,1.00)	0.89 (0.84,0.93)
Psychiatric	1.28 (1.20,1.35)	1.29 (1.21,1.36)
Ophthalmological	1.40 (1.35,1.46)	1.37 (1.32,1.42)
Infections	1.29 (1.24,1.33)	1.26 (1.22,1.31)
Fragility fracture	1.18 (1.11,1.25)	1.14 (1.08,1.21)

Composite outcomes

Cox proportional hazard analysis was used to assess whether the differences observed in the incident rate of comorbidities after index date were significantly different in patients with or without PMR. Most of the observed differences in incidence of composite outcomes, either increased or decreased, were found to

be significant. These results remained after adjustment for BMI category, smoking status, alcohol consumption, age and sex.

The composite outcomes for which there was a statistically significant increased risk in patients with a diagnosis of PMR included vascular, respiratory, gastroenterological, autoimmune, endocrine, psychiatric, ophthalmological and infectious diseases, as well as fragility fractures. The largest effect size was seen with autoimmune conditions, for which a hazard ratio [HR] of 4.68 [95% confidence interval (CI) 4.35, 5.03] was calculated.

The risk of cancer diagnosis was not found to be significantly different in cases or controls [HR 0.98 (0.94, 1.01)]. However, after adjustment for BMI, alcohol consumption and smoking, the risk of neurological diseases were found to be significantly reduced [HR 0.89, (0.84, 0.93)].

To examine these findings in greater detail, the stratified outcomes are tabulated in table 6-18. They are also graphically presented, with the total number of new diagnoses in patients with PMR indicated also, in figures 6-3 and 6-4 for ease of interpretation. In these figures, autoimmune outcomes are not included as the hazard ratios were far greater than one.

Table 6-18: Hazard ratios (including 95% confidence intervals) illustrating likelihood of stratified comorbidities following index date

	HR (unadjusted)	HR (adjusted)
Cancer		
Breast cancer	0.87 (0.78, 0.98)	0.88 (0.79, 0.98)
Prostate cancer	1.17 (1.04, 1.30)	1.11 (0.99, 1.24)
Lung cancer	0.86 (0.77, 0.95)	0.86 (0.77, 0.95)
Colon cancer	0.97 (0.87, 1.08)	0.95 (0.85, 1.06)
Melanoma	0.99 (0.82, 1.19)	0.96 (0.80, 1.15)
Leukaemia, lymphoma	1.15 (1.02, 1.28)	1.11 (0.99, 1.25)
Vascular		
CVD	1.32 (1.26, 1.39)	1.30 (1.24, 1.37)
CCF	1.30 (1.23, 1.37)	1.25 (1.19, 1.32)
PVD	1.47 (1.38, 1.58)	1.44 (1.35, 1.55)
CVA	1.10 (1.05, 1.16)	1.07 (1.02, 1.12)
HTN	1.22 (1.17, 1.27)	1.21 (1.16, 1.25)
Respiratory		
Asthma	1.24 (1.15, 1.35)	1.25 (1.15, 1.35)
COPD	1.22 (1.14, 1.29)	1.23 (1.15, 1.30)
Lung fibrosis	1.57 (1.35, 1.82)	1.50 (1.29, 1.75)
Renal		
Renal disease	1.39 (1.35, 1.44)	1.34 (1.30, 1.39)
Gastroenterological		
Moderate liver disease	1.09 (0.94, 1.27)	1.09 (0.94, 1.27)
Peptic ulcers	1.13 (1.01, 1.27)	1.11 (0.99, 1.25)
Crohn's disease	1.52 (0.99, 2.33)	1.52 (0.98, 2.33)
Ulcerative colitis	1.72 (1.45, 2.04)	1.71 (1.44, 2.03)
Autoimmune and musculoskeletal		
SLE	4.42 (2.77, 7.05)	4.65 (2.92, 7.40)
Systemic sclerosis	2.20 (1.20, 4.06)	2.23 (1.21, 4.14)
Rheumatoid arthritis	6.90 (6.27, 7.60)	6.99 (6.35, 7.70)
Sjogren’s syndrome	2.95 (2.09, 4.18)	3.07 (2.16, 4.35)
Psoriatic arthritis	8.03 (6.31, 10.22)	8.23 (6.46, 10.47)
Raynaud's disease	1.48 (1.27, 1.72)	1.47 (1.26, 1.71)
Osteoarthritis	1.93 (1.86, 2.00)	1.90 (1.83, 1.97)
Endocrine		
Hyperthyroidism	1.41 (1.20, 1.65)	1.41 (1.20, 1.66)
Hypothyroidism	1.25 (1.16, 1.34)	1.25 (1.16, 1.34)
T1DM	1.54 (1.12, 2.11)	1.53 (1.11, 2.10)
T2DM	1.51 (1.43, 1.59)	1.49 (1.42, 1.57)
Addison's disease	4.00 (2.47, 6.49)	4.01 (2.48, 6.48)
Neurological		

	HR (unadjusted)	HR (adjusted)
Dementia	0.93 (0.88, 0.98)	0.87 (0.82, 0.92)
Parkinson's disease	1.07 (0.94, 1.23)	1.04 (0.90, 1.19)
MS	1.16 (0.51, 2.68)	1.20 (0.52, 2.74)
Psychiatric		
Bipolar disease	1.15 (0.68, 1.94)	1.20 (0.71, 2.03)
Depression	1.40 (1.31, 1.49)	1.41 (1.32, 1.50)
Anxiety	1.18 (1.10, 1.27)	1.19 (1.11, 1.28)
Schizophrenia	0.95 (0.58, 1.57)	0.97 (0.59, 1.60)
Complications due to glucocorticoids		
Osteoporosis	2.12 (2.03, 2.21)	2.11 (2.03, 2.20)
Hip fracture	1.09 (1.02, 1.17)	1.05 (0.98, 1.13)
Wrist fracture	1.14 (1.04, 1.25)	1.13 (1.03, 1.24)
Vertebral fracture	2.05 (1.73, 2.42)	1.96 (1.66, 2.32)
Ophthalmological		
Cataracts	1.41 (1.36, 1.47)	1.37 (1.32, 1.43)
Glaucoma	1.28 (1.18, 1.37)	1.25 (1.16, 1.35)
Infections		
UTI	1.25 (1.21, 1.31)	1.23 (1.18, 1.28)
URTI	1.27 (1.22, 1.31)	1.25 (1.20, 1.29)
LRTI	1.22 (1.15, 1.29)	1.18 (1.12, 1.25)
Skin infections	1.36 (1.31, 1.42)	1.33 (1.28, 1.38)

Figure 6-3: Likelihood of comorbidities after index date expressed as hazard ratios with 95% confidence intervals (unadjusted)

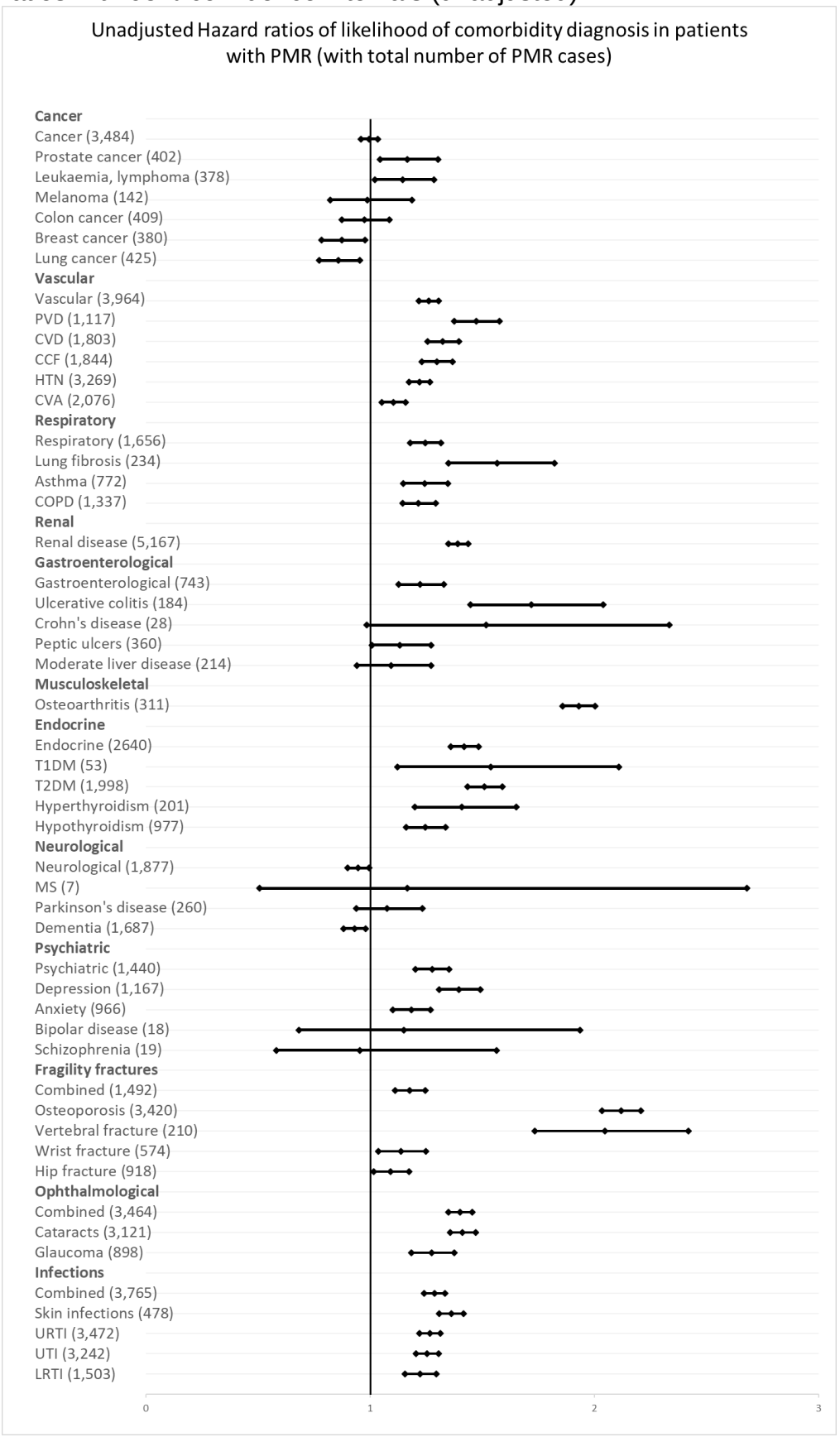
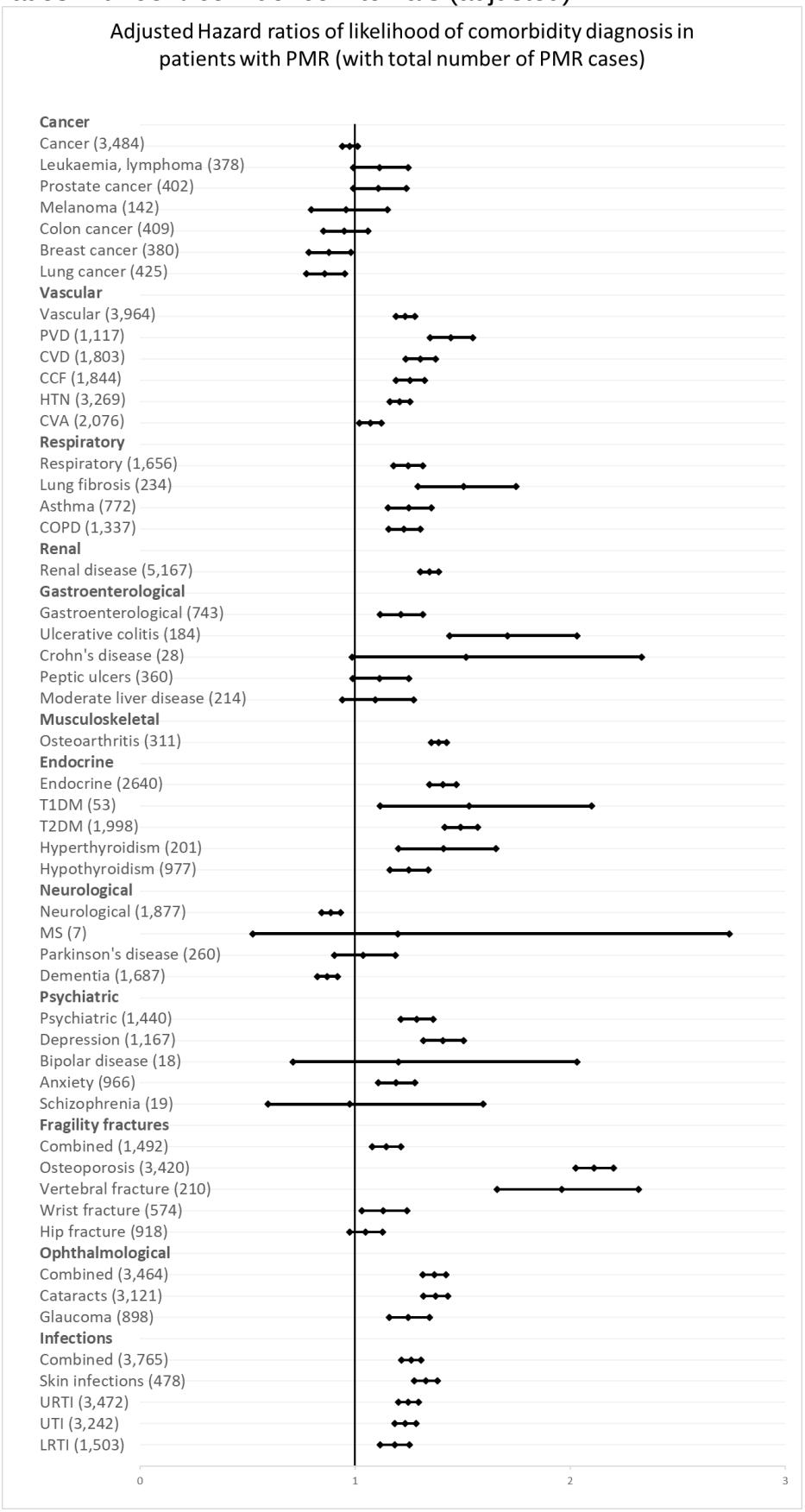


Figure 6-4: Likelihood of comorbidities after index date expressed as hazard ratios with 95% confidence intervals (adjusted)



Stratified outcomes

Cancer

Of the six main cancer types, after adjustment for alcohol consumption, BMI category, age, sex and smoking status, two show no significant difference in diagnosis subsequent to index date (prostate cancer and melanoma), while four show a statistically significant reduction in the likelihood of diagnosis (leukaemia or lymphoma and colorectal, breast and lung cancers). The biggest reduction seen was in the risk of diagnosis of lung cancer in patients with PMR, where it dropped by 20%. Overall, however, the composite risk of cancer was not significantly reduced.

Vascular

After adjustment, all of the vascular outcomes were significantly more likely to occur after index date in patients with PMR. These included peripheral and cardiovascular disease, as well as congestive cardiac failure, hypertension and cerebrovascular disease.

Comorbidities linked to GC prescription

Most of these conditions, which included ophthalmological diagnoses such as cataracts and glaucoma, as well as osteoporosis, fragility fractures, and infectious diseases were significantly more likely to occur in patients with a previous diagnosis of PMR both before and after adjustment was applied. The

single exception to this was hip fractures, where no significant difference in the likelihood of development of this comorbidity was seen, albeit only in the adjusted group.

Other comorbidities

All of the comorbidities within the respiratory category, including lung fibrosis, asthma and COPD were statistically significantly more likely to be diagnosed in patients who had a pre-existing diagnosis of PMR. The risk of diagnosis with renal disease and all of the autoimmune comorbidities investigated, was also found to be significantly higher in patients with PMR.

The risk of diagnosis with all endocrine comorbidities was found to be higher in patients with PMR. Specifically, the risk of Addison's disease, hypothyroidism, hyperthyroidism and type 1 and 2 diabetes mellitus were all significantly higher in patients with PMR. However, in the case of gastroenterological comorbidities, a more mixed picture emerged. The risk was significantly higher in the case of ulcerative colitis, however there was no significant difference in the risk of Crohn's, peptic ulcer and liver disease between patients with or without PMR.

Patients with PMR were statistically significantly less likely to be diagnosed with dementia. No significant difference was seen between patients with PMR compared to those without in the risk of developing Parkinson's disease or multiple sclerosis (MS). Regarding psychiatric diagnoses, similar to what was found in the case control study, the more common psychiatric diagnoses of anxiety and depression, which include cases of mild and moderate severity, were

significantly more likely to have occurred in patients who had a diagnosis of PMR. However, in the case of psychiatric illnesses that could be perceived as ‘more serious’, such as schizophrenia and bipolar disease, no significant difference in risk was observed.

6.4 Discussion

6.4.1 Main findings

This study has found that patients with PMR have a higher rate of comorbid diseases when compared to matched controls prior to, and after, diagnosis of PMR. There was a significantly increased risk of vascular, respiratory, renal, autoimmune, endocrine and psychiatric diseases both before and after index date in patients with PMR. Conversely, the risk of cancer and dementia was significantly lower in patients with PMR compared to their matched controls. These differences were again present before and after index date. Finally, following index date, the risk of glucocorticoid (GC) related conditions was higher in patients with PMR when compared to those without.

This study is the first to provide a broad, comprehensive view of comorbidities in patients with PMR compared to matched controls and will inform discussion around whether the presence of certain comorbidities should indeed preclude its diagnosis.

6.4.2 Charlson comorbidity index

Both before and after diagnosis, an increased proportion of cases had a higher Charlson comorbidity index score. At the same time, the proportion of controls with a Charlson score of zero was greater. However, at most time points before and after index date, a greater proportion of controls had a Charlson index score of 5 or more, although the absolute number of patients were small. This indicates

that patients with PMR had, on average, a greater burden of comorbid disease, but also that patients with the highest burden of comorbidities were less likely to be diagnosed with PMR.

6.4.3 Strengths and limitations

This is the largest study investigating the association of PMR with a broad range of comorbidities both before and after a diagnosis of PMR. The comorbidities were selected using robust methodology and the data sample used comes from a large, established database of patients who are representative of the UK population. (Williams et al., 2012) Furthermore, as the majority of patients with PMR are managed exclusively in primary care, the patients are likely to be representative of people diagnosed with PMR. (Barraclough et al., 2008; Yates et al., 2016) Therefore, this is the most appropriate setting to conduct this study.

As discussed in chapter 3, a potential limitation is ascertainment of cases. For PMR, the authenticity of these diagnoses is reinforced by requiring that all cases have at least two GC prescriptions as well as an appropriate medical code. This method has been used before in previously published studies in CPRD of PMR. (Smeeth, Cook and Hall, 2006; Hancock et al., 2014; Muller et al., 2014)

The code lists used in these studies were, when possible, updated versions of lists previously composed for use in similar studies that used CPRD to estimate the risks of vascular disease, cancer and fragility fractures. (Hancock et al., 2014; Muller et al., 2014; Paskins et al., 2018) These lists were obtained with the authors' consent, and meticulously checked for accuracy by two authors, (RP &

AAS) as discussed in chapter 2.11. Of the remaining conditions, for which no existing list was available, new lists were produced using the CPRD medical code browser and reviewed by two authors (RP & AAS), one of whom has a clinical background, the other who is an epidemiologist.

In order to ensure as many patients were included in the study, there was no requirement for follow up after index date. This meant that patients who had a higher disease burden and may have been more likely to die close to index date were kept in the study. If there had been a minimum requirement for follow up after index date then these patients, with a higher burden of comorbidity, would have been excluded.

Incomplete data is a potential limitation of this study, particularly when using covariates such as BMI, alcohol and smoking to produce adjusted odds and hazard ratios. In this study, 13.7% of patients had no record of alcohol consumption, 13% BMI measurement and 5.8% smoking status. The proportion of patients without this data is improved compared to previous CPRD studies, in which around 20% of patients had no alcohol or BMI data recorded. (Herrett, Bhaskaran, et al., 2015) Furthermore, the proportion of missing data in this observational study of routinely collected health records compares favourably to other methods of data collection, such as surveys. (Coste et al., 2013) It is likely that patients without data are healthier, with lower rates of smoking, alcohol excess or obesity. This is because it is more likely that primary care healthcare teams would record this information in patients who smoked, drank excess amounts of alcohol or were obese.

Another potential limitation is a consequence of the deliberate desire to maintain the broad scope of this study. By examining such a wide range of comorbidities, there is the potential to find significant results due to the number of comparisons made. This is known as a Type I error, or an error caused by multiple testing. As the confidence intervals were set to 95%, one in twenty tests undertaken would therefore produce a significant result through chance alone. In mitigation of this the aim of this study was to assess for possible associations between PMR and other comorbidities, it was not designed to prove causation. By investigating the overall health of patients with PMR and examining for potential trends in comorbidity prevalence, potential areas for future research could be identified. The broad range of comorbidities and the relatively advanced average age of study participants also meant that some of the conditions assessed were rare, in the prospective study, where patient's previous diagnoses were excluded. This meant that for these comorbidities, the analyses were underpowered to find significant associations, but because the case control study looked retrospectively, the overall risk of comorbidities could still be ascertained.

Finally, the other main risks of bias in this study were surveillance bias and diagnostic overshadowing. Surveillance bias occurs where a patient within the case, or exposure group, are subject to increased surveillance, examinations or investigations compared to controls. In this study, patients with PMR, due to either the prodromal features of PMR, or increased follow up after diagnosis, including regular blood tests, will be at increased risk of comorbidities being identified compared to the control group. This effect has been seen in different specialities. An observational study of patients following a diagnosis with renal calculi found that they were subsequently more likely to be diagnosed with cancer

at a variety of sites, and that this increase persisted for up to ten years following index date. (Hemminki et al., 2017)

Diagnostic overshadowing is a concept that is commonly linked to psychological or psychiatric conditions. In this, physical symptoms that a patient may complain of are inadvertently to their psychiatric illness. (Shefer et al., 2014) It may be that this effect takes place when those with an existing serious psychiatric or neurological disease, such as schizophrenia or dementia, present with symptoms of PMR. The symptoms may then be attributed entirely to the existing condition rather than PMR. However, diagnostic overshadowing might just as easily affect other serious medical conditions; for example, this effect may also be a factor in the apparent reduction in the risk of cancer in patients with PMR. Cancers can cause constitutional symptoms similar to PMR, and, as discussed previously, this fact is explicitly taken into account in the clinical classification criteria in PMR. (Dasgupta et al., 2010, 2012) In these criteria it is suggested that conditions such as cancer should be excluded in patients presenting with suspected PMR.

6.4.4 Comparison to other studies

Vascular disease

As discussed in chapter five, there have been eight previous studies that assessed the risk of vascular disease, prospectively, following a diagnosis with PMR. (B.-Å. Bengtsson and Malmvall, 1981; Kremers et al., 2005; Kang, Sheu and Lin, 2011; Kermani and Warrington, 2011; Zoller et al., 2012; Zöller et al., 2012; Hancock et al., 2014; Pujades-Rodriguez et al., 2016) These studies

reported a range of outcomes. Most of these studies found an increase in the risk of vascular disease in patients with PMR.

One of the two largest studies, by Hancock et al. (2014) used the GPRD dataset, a precursor of the CPRD database. In this paper, the adjusted hazard ratio [95% CI] of first vascular event was 2.6 [2.4, 2.9]. This is much greater than in the current study where the equivalent result was 1.23 [1.19, 1.28]. The effect size in this study was similar retrospectively, where the odds ratio of any vascular disease prior to diagnosis was 1.04 [1.01, 1.07]. Both of the observed increases in risks were statistically significant however. The study from Hancock et al (2014) utilised a smaller sample size (n= 3,249) and was drawn from patients with a diagnosis of PMR between 1987 and 1999. The larger sample size and more recent data collection in this study may account for the reduction in effect size.

A second, more recent, study by Pujades-Rodriguez et al. (2016) found a significant overall reduction in the risk of vascular diseases (incidence rate ratio 0.88 [0.83,0.94]). This study was drawn from the CALIBER (CArdiovascular disease research using LInked Bespoke studies and Electronic Health Records) dataset. This database links 225 primary care practices to hospital and mortality data. In their study, the number of PMR cases was smaller than the current study (n=9,776), as was the number of controls (n=105,504), even though each PMR patient was matched to more (up to 10) controls. The other main difference with this and the current study was the total median follow up after index date for the Pujades-Rodriguez paper of 3.1 years, compared to 5.0 years in the current study.

The difference in results between the apparent reduction in risk of vascular disease in Pujades-Rodriguez's (2016) study and the current study could be for a number of reasons. As discussed in chapter 5, Pujades-Rodriguez (2016) did not use a strict age inclusion criteria, patients aged over 18 were included, rather than the higher threshold of forty years employed in this study. Alternatively the difference in follow up or the larger sample size may allow more accurate assessment of the risk. Finally, the main endpoints reported in this study, that of composite outcomes of coronary and death or fatal and non-fatal cardiovascular disease take into account mortality data. However, when only patients with pure PMR and any vascular outcome were considered, the proportion of PMR cases who developed a vascular outcome was indeed higher, (23.2%) compared to those without (20.4%).

This proportion was less that what was seen in the current study where, after two years of follow up, 38.9% of cases and 35.1% of controls had at least one record of vascular disease in their notes. The difference in these proportions can be explained as, similar to Hancock et al (2014), patients in the Pujades-Rodriguez (2016) study were intentionally vascular disease free at outset. However, this was not the case in the current study when cumulative probability was calculated, in order that the most accurate representation of disease burden be described. Furthermore, although the absolute numbers are much higher in the current study, the difference in the proportion of PMR cases and controls with a vascular disease was similar in both studies, at 2.8% for Pujades-Rodriguez and 3.8% in the current study.

Cancer

Six studies (Haga et al., 1993; Myklebust et al., 2002; Jianguang et al., 2010; Muller et al., 2014; Pfefiffer et al., 2015; Bellan et al., 2017) have previously estimated the risk of cancer in patients after diagnosis with PMR. Two found a higher proportion of patients with PMR subsequently developed cancer, two were equivocal, while two found the opposite. In the current study, the risk of cancer prior to index date was lower in patients with PMR (Odds ratio 0.89 [0.86, 0.93]) although this reduction in risk was not observed subsequent to index date (Hazard ratio 0.98 [0.94, 1.01]).

After ten years of follow up, around 40% of cases and controls had been diagnosed with cancer. The mean follow up after index date was 4 years for both cases and controls. Therefore, ten years after the index date, the study sample had reduced significantly. However, this correlates well with estimates that half of the UK population will be diagnosed with cancer during their lifetime. (Cancer Research UK 2019)

Upon stratification of cancer risks, it can be seen that the risk of most of the outcomes, particularly breast, colorectal, leukaemia, lymphoma and lung was higher in controls rather than cases. It may be, in this case, that this is due to diagnostic overshadowing as discussed earlier. The single cancer with a consistently increased rate among patients with PMR was prostate cancer. As PMR predominantly affects women and prostate cancer exclusively affects men, this apparent increase in risk could be erroneous.

The only previous study of UK primary care data was carried out in GPRD, this was the forerunner of CPRD. In this study, the risk of cancer diagnosis was higher

in the first six months after diagnosis before returning to the baseline rate. The differences in this study included that it used an earlier iteration of CPRD and had a smaller sample size (n= 12,819 total). As well as that, all the patients identified were vascular disease free at outset. These factors may have contributed to the differences in results. Shared risk factors between vascular disease and certain cancers exist, for example smoking increases the risk of vascular disease and a large number of cancers, particularly lung, excluding these patients may have introduced bias into the study design.

Autoimmune conditions

As discussed in chapter one, whether PMR is an autoimmune or auto-inflammatory disease remains a matter of debate. (Floris et al., 2018) One study categorised immunological diseases into either autoimmune or auto-inflammatory. (McGonagle and McDermott, 2006) Of the comorbidities assessed in the current study, thyroid diseases, rheumatoid arthritis (RA), Sjogren's disease, systemic lupus erythematosus (SLE) and systemic sclerosis (SS) were all categorised as polygenic autoimmune conditions. Crohn's disease, ulcerative colitis, type one diabetes and osteoarthritis were proposed to be polygenic auto-inflammatory diseases, while psoriatic arthritis was classified as mixed.

Applying this to the results from this study, of the autoimmune diseases, thyroid diseases, RA and Sjogren's disease were strongly associated with PMR diagnosis both before and after index date. The picture was more mixed in the case of SLE and SS however, where the retrospective increase in the risk of diagnosis in patients who went on to develop PMR did not reach statistical

significance. Of the auto-inflammatory conditions, ulcerative colitis and osteoarthritis were statistically significantly associated with PMR both before and after index date, as indeed was psoriatic arthritis. However, no significant difference was observed with type one diabetes and Crohn's disease.

Overall, these results provide more evidence that PMR should be grouped as an immunological condition. However, whether it ought to sit within the subcategories of autoimmune or auto-inflammatory is less clear. Complicating the picture is a number of factors. The first is misdiagnosis, for example, although OA is an auto-inflammatory condition and is strongly linked to PMR, the presenting features of both conditions- pain, aching and stiffness are very similar. Furthermore, although OA is traditionally thought of as non-inflammatory, it is well recognised to have an inflammatory component. (Glyn-Jones et al., 2015)

The issue of misdiagnosis between PMR and RA, particularly Elderly-onset rheumatoid arthritis (EORA), was discussed in chapter 1 and could be part of the reason why such a strong link with PMR, particularly prospectively, was found. In this case, patients with an existing diagnosis of PMR and difficulty reducing GC were perhaps then investigated further and later received a diagnosis of RA. Other associations that were not found to be significant, for example between PMR and SLE or SS were likely a reflection of those conditions' rarity and the relative rarity of PMR. In these conditions, although the rate of diagnosis was higher in patients with PMR, there were insufficient numbers, and therefore power, for significant differences to be observed.

Previous research into whether PMR co-exists with other autoimmune conditions was performed by Eaton et al. (2007). In this study, PMR was included within an

epidemiological study of 33 autoimmune conditions in Denmark. Consistent with the findings in this study, an increase in the risk of Sjogren's disease, SLE, SS, psoriatic arthritis, ulcerative colitis and Crohn's disease was found. However, this study also investigated, and found an increase in, the risk of multiple sclerosis (MS). This contrasts with the current study in which the risk of MS was significantly reduced both before and after index date. Similar to cancer diagnoses, this reduction may have been due to diagnostic overshadowing.

Some work has also been done around the risk of thyroid disease in patients with PMR, (Bowness et al., 1991; Juchet et al., 1993) the results of which were equivocal. This contrasted with this study where the risk of both hypo- and hyperthyroid disease was greater before and after index date in patients with PMR.

The results from this study support the conclusion that PMR should be categorised as an immunological disease. However, the statistically significant associations which exist across both autoimmune and auto-inflammatory conditions make it difficult to firmly subcategorise PMR at this point in time.

Glucocorticoid related conditions

Shbeeb et al. (2018) published a cohort study of 359 patients with PMR and an equal number of comparators, investigating the likelihood of GC related complications (including diabetes mellitus, hypertension, cataracts and fragility fractures). The controls in the study were subjects without PMR who were matched by age and sex. They found a statistically significant increase only in

the incidence of cataracts over the median follow up period of 5.8 years hazard ratio (HR) 1.72 [1.23, 2.41]. All of the other measured outcomes were found to be non-significantly reduced (diabetes mellitus, hypertension and hip or any other fracture) or increased (hyperlipidaemia and vertebral or Colles fractures). Paskins et al. (2018) published a CPRD based study into patients with PMR and GCA, and found an increase in the rate of fragility fractures.

In this study, similar to Paskins et al, the risk of any fragility fractures was found to be higher in patients with PMR. Within the stratified outcomes, the risk of vertebral fracture was significantly higher in patients with PMR, while the risk of hip fracture was less in those with PMR. Interestingly, a similar pattern of an increase in the risk of vertebral fracture and a reduction in the risk of hip fracture in patients with PMR was observed by Shbeeb et al (2018). Furthermore, this study replicated their findings of an increased risk of cataracts and also found an increase in the risk of glaucoma, which was not assessed by Shbeeb et al (2018). However, contrary to Shbeeb et al's (2018) findings, the risk of type two diabetes was significantly higher in patients with PMR in this study.

In this study, the risk of osteoporosis was found to be higher in patients with PMR, however the risks of each type of fragility fracture was more mixed. It may be that GPs are alert to the dangers of long term GC treatment in PMR and therefore intervene to reduce the risk of fragility fractures by providing more active and earlier treatment, such as bisphosphonate medication.

Other GC related outcomes, specifically those linked to infectious diseases, have not previously been reported. As would be expected, given the

immunosuppressant properties of GCs, the rates of infectious diseases were all found to be significantly higher in patients with a history of PMR.

Other comorbidities

Psychiatric comorbidity

Previous studies have found no association between PMR and psychiatric comorbidities such as schizophrenia (Eaton et al., 2006; Chen et al., 2012) and bipolar disease, (Eaton et al., 2006). In this study, patients with PMR were actually observed to have a significantly reduced risk of diagnosis with schizophrenia prior to index date. This may be due to diagnostic overshadowing. Schizophrenia is a severe, enduring disorder that is known to cause disability, as well as cognitive and functional impairment. (Grande et al., 2016; Owen, Sawa and Mortensen, 2016)

The risk of depression and anxiety was found to be higher in patients with PMR, which is perhaps linked to the chronic nature of the pain and stiffness associated with PMR. Furthermore, it is well established that depression is linked to multimorbidity (Read et al., 2017) and, as has been established in this study, patients with PMR have higher rates of comorbidities compared to controls. A recent postal study of a cohort of 704 patients in the UK with a diagnosis of PMR within the last three years confirmed that 15% of patients reported current depressive symptoms. (Vivekanantham et al., 2018)

Neurological comorbidity

One previous study found an increase in the risk of Parkinson's disease in patients with PMR. (Kari Hemminki, Li, et al., 2012) However, the current study found the risk of Parkinson's disease, MS and dementia was significantly lower in patients with PMR prior to index date. After index date, the risk of dementia was significantly reduced, however no significant difference was seen in the risk of MS or Parkinson's disease. Again, it may be that the rates of PMR in patients with these conditions are similar, but, due to diagnostic overshadowing, PMR is under-diagnosed in these groups. Although not specifically relating to PMR, it is becoming better recognised that that chronic pain in elderly patients with cognitive decline is under-diagnosed. (Cravello et al., 2019)

A number of reasons for this could be postulated, for example communication difficulties as a result of cognitive impairment, or, even when a history of aching or pain is elicited, GPs downplaying them or viewing them as part of the disease process in dementia. Furthermore, the converse could also be true, that patients who do not have another serious condition may be more likely to receive a diagnosis of PMR. In this case, patients who present to GPs with vague, poorly localised symptoms such as myalgia, stiff joints or tiredness may be more likely to receive a diagnosis of PMR because of the absence of another definable cause.

Rather than the apparent associations seen in this study being entirely due to biological factors, it may be that human factors around competing health priorities and the short amount of time GPs have to make clinical decisions mean that certain comorbidities appear less frequently in patients with PMR. These possible

complicating factors might also have an effect on the possible associations between other comorbidities and PMR, such as cancer.

Endocrine comorbidity

Conditions within this category have been discussed previously as either autoimmune or relating to GC usage. The risk of diagnosis of Addison's disease may be higher in patients with PMR, but, despite the size of this study, there was insufficient statistical power to show a significant association.

Renal and Respiratory comorbidities

As discussed in chapter 5.4, the existing literature does not contain estimates of the risk of respiratory and renal diseases in patients with PMR. As such, this is the first study to estimate these figures. From this data, it appears that the risk of renal disease, asthma, lung fibrosis and COPD are significantly higher in patients with PMR both prior to, and following, index date. There could be a number of reasons for this difference. Among these could be surveillance bias, links to pathological processes or shared immunological processes.

Surveillance bias could explain the increased risk of diagnosis with renal disease. Patients with PMR are likely to have regular blood tests as part of their follow up, and given that it has been estimated that up to one million people in the UK may have undiagnosed renal disease, (Kerr et al., 2012) it may be simply that PMR follow up means these patients are more likely to be identified.

The increased risk of diagnosis with asthma in patients with PMR could be due to shared immunological pathways. Asthma and PMR are both conditions that are characterised by inflammation, responsiveness to GC treatment and possibly an autoimmune cause. (Tedeschi and Asero, 2008) Similarly, although the cause of pulmonary fibrosis can be occupational, it is often idiopathic and, similar to PMR it displays some responsiveness to GC therapy. (Richeldi, Collard and Jones, 2017) Therefore there may be some shared immunological processes and it is conceivable that this could in part account for some of the observed increase in risk of asthma and lung fibrosis in patients with PMR.

6.4.5 Conclusion and clinical implications

This study is the first to estimate total disease burden in patients with PMR before and after diagnosis. In conclusion, patients with PMR have a greater number of comorbidities when compared to matched controls prior to, and after, diagnosis. Specifically, the risks of vascular, renal, respiratory and psychiatric conditions are increased, as are the risks of GC related comorbidities. Reassuringly, however, the risks of cancer and neurological diseases appear to be significantly less in patients with PMR, although, as discussed previously, this apparent reduction in risk may be due to ascertainment bias.

The associations between certain comorbidities and PMR that have been observed in this study mean that practical recommendations could be made in the management of PMR.

1. Increased surveillance for important comorbidities in patients with a diagnosis of PMR.

Some of the comorbidities which are seen to be at higher risk in patients with PMR may have been detected due to surveillance bias. However, others, such as vascular disease and psychiatric comorbidities such as depression and anxiety, may be due either to the inflammatory pathophysiology of PMR, the symptoms caused by the disease itself or even the treatment for it. As such, patients with a diagnosis of PMR need to be screened thoroughly for the development of these conditions.

Furthermore, given these observed associations between PMR and vascular disease, practitioners need to emphasise the importance of timely reduction and withdrawal of GC therapy where possible. Also, maintaining a holistic approach, through advising smoking cessation, diet management as well as active blood pressure and cholesterol control should be stressed.

2. Confirmation that PMR can exist alongside other immunological diagnoses.

Immunological conditions cluster together and this study has confirmed that the presence of PMR greatly increases a patient's chances of a diagnosis with another immunological condition. Some of these diagnoses may be misclassifications, where patients with PMR go on to be re-diagnosed with

another condition such as RA. However, this study has shown that patients with PMR also have an increased risk of immunological conditions prior to index date. PMR should be regarded as an immunologically mediated disease and no longer as a diagnosis of exclusion.

3. PMR should be considered more strongly in patients with existing cancer or neurological diagnoses.

In patients with PMR a previous diagnosis of either cancer or a serious neurological disease, PMR is much less likely to be diagnosed. It may be that some of these potential PMR cases are missed due to diagnostic overshadowing. Therefore, it could be argued that current clinical classification criteria, which note that the presence of these comorbidities may preclude a diagnosis of PMR, perhaps ought to be challenged.

The next chapter involves an analysis of a subset of these patients in this study. It will look at linked data on admissions to hospital, including reasons for admission, as well as mortality data taken from linked datasets in order to assess whether the observed differences in morbidity rate affect hospital admission or mortality in patients with PMR.

Chapter 7 COMORBIDITIES IN POLYMYALGIA RHEUMATICA: SECONDARY CARE LINKED DATASETS

This chapter contains the results of three studies. The first is a prospective analysis of the rate of hospital admissions after index date in patients with PMR compared to matched controls. The second is a retrospective case control and prospective cohort analysis of the reasons for hospital admission before and after index date in the same patient sample. The third study in this chapter is a prospective mortality analysis, again comparing patients with PMR to matched controls. These studies will be carried out using datasets linked to the CPRD.

7.1 Introduction

In the previous chapter it was established that patients with polymyalgia rheumatica (PMR) have a greater number of comorbidities than patients who were matched by age, sex and practice, on their primary care electronic health records. It was found that patients with PMR were more likely to have a recorded diagnosis of vascular, respiratory and autoimmune conditions. Conversely, it was demonstrated that patients with PMR were less likely to have a recorded diagnosis of neoplastic and dementia.

CPRD contains data collected and coded within primary care. Many of the comorbidities previously studied are diagnosed and managed in primary care. However, some comorbid conditions investigated are diagnosed and managed largely in secondary care. Although, due to the 'hub and spoke' model of the NHS, even these types of conditions, such as myocardial infarctions, should also

be recorded in primary care electronic medical records. This study will assess secondary care data to assess the impact of the greater burden of comorbidities seen in the previous chapter on the health of patients with PMR.

This chapter will investigate the prevalence and likelihood of admission to hospital, with a comorbidity, in patients with PMR compared to their matched controls using data taken from secondary care. In addition, the mortality rate of patients with PMR will be compared to those without. The databases used in this study will be Hospital Episode Statistics (HES) and the Office for National Statistics (ONS). From these datasets, information can be obtained regarding the number of hospital admissions, primary reasons for hospital admission, mortality rates and causes of death.

The use of linked data will allow the testing of a number of hypotheses. The first uses HES data to investigate whether the increased rate of comorbidities in primary care data in patients with PMR is translated to differences in hospital admission rates or reasons for admissions. The second aim is to investigate whether differences in comorbidities diagnosed in primary and secondary care are associated with differences in mortality rates and causes of death in patients with PMR compared to matched controls.

7.1.1 Data Linkage

Of the practices contributing data to CPRD, only practices based in England are eligible for linkage to further datasets. Of those practices, 75% have consented to link data. (Herrett, Bhaskaran, et al., 2015) Where consent exists, patient level data is linked via NHS Digital (previously known as the Health and Social Care

Information Centre) to other established data sources. (NHS Digital) NHS Digital is regarded as a trusted third party and anonymises data from hospitals and CPRD to ensure security of patient information.

The linkages between CPRD and other datasets have been established at different times. Hospital Episode Statistics (HES) data can originate from as early as 1997 and at the time the data was analysed runs until December 2017. Death registration data, from the Office for National Statistics, is available from January 1998 until February 2018. Each linked dataset will now be considered in turn.

7.1.2 Hospital Episode Statistics

Hospital Episode Statistics (HES) is a database that contains coded information from secondary care linked to patients contributing to CPRD. This database provides information on hospital admissions for linked patients across a number of domains.

Similar to the main CPRD database, the primary recorded diagnosis in the linked data is recorded as a code. However, instead of using the Read code classification system, the International statistical classification of diseases and related health problems (ICD) 10 system is used. The ICD 10 system is maintained by the World Health Organisation and has been in use since 1994. It contains codes for diseases, which will be used in this study, and also for symptoms, signs, social findings and a number of other domains. The code is hierarchical and consists of a letter followed by two numbers before a full stop. For example codes beginning with the letter ‘C’ or ‘D’ encompass all neoplastic

diseases. For greater specificity more numbers, after the full stop, can be employed, for example C75.1 refers specifically to a malignant neoplasm of the pituitary gland. (World Health Organisation, 2016) The comorbidities which will be investigated in this study will be the same as those identified in chapter 6, the investigation into comorbidities in patients with PMR in primary care.

Currently, there are few studies in medical literature wherein data on rates of hospital admissions in patients with PMR have been published. In 2018, an abstract was presented at the American College of Rheumatology annual meeting, where information around hospital admission rates, diagnoses made, duration and readmissions in patients with PMR, who were identified in the Olmsted County cohort, were described and compared to matched controls. No significant differences were observed in this cohort. (Raheel et al., 2018) These findings have not yet been published in a peer reviewed journal however.

One further piece research is a study using Hospital Episode Statistics which was published as a 'letter to the editor' in Rheumatology. In this, it was reported that the rates of admission in the UK due to either giant cell arteritis (GCA) or PMR was increasing over time, from 2002-2013. However, rates of sight loss were not reducing. (Mollan et al., 2015) As there is a paucity of research in this field, it is important to address the rate of admission to hospital among patients with PMR and, further to this, the reasons for admission.

There are a number of existing studies into comorbidities in patients with PMR which are based on national registries of hospital admission data and were described in chapter 5. However, these studies, which are mainly based in Scandinavia, also used hospital admission data as the basis for identification of

cases of PMR. This could underestimate the true prevalence of PMR and also lead to the exclusion of patients with less severe PMR because, as previously discussed, the majority of patients with PMR are diagnosed and managed in primary care and, as advised in guidance, only referred for specialist review at times of atypical clinical presentation. (Barraclough et al., 2008; Yates et al., 2016)

One existing study, which used a primary care dataset linked to secondary care data, was an investigation into whether PMR was associated with vascular disease. (Pujades-Rodriguez et al., 2016) In this study, a higher proportion of patients with PMR developed vascular disease. However, overall, when outcomes such as mortality due to vascular disease was included, PMR patients actually fared better than their matched controls.

This study will utilise a linked national database that covers all hospital admissions in England. It will investigate the rate of, and reasons for, hospital admissions in patients with a diagnosis of PMR in their primary care records, compared to matched controls. This will provide a more accurate estimate of the true rate of hospital admission and reasons for this in all patients with PMR, rather than only those who have perhaps a more severe subset of PMR and were diagnosed in secondary care. In carrying out this study, the aim will be to assess the validity and severity of the differences in comorbidity prevalence described in chapter 6, by assessing the degree to which the increased levels of comorbid disease impacts on levels of healthcare utilisation.

7.1.3 Death Registration data

Using linked death registration data, from the Office for National Statistics (ONS) this study will estimate survival in patients with PMR compared to matched controls.

Death registration data linked to CPRD currently covers the period from January 1998 until February 2018. This dataset contains information on the official date of death, the date of registration of death as well as the underlying cause of death and any other contributing factors given. (Dedman et al., 2018)

As discussed in chapter 5, the impact of PMR on mortality has been reported in four studies. Of these, three found a reduced mortality among patients with PMR, (Gran et al., 2001; Doran et al., 2002; Myklebust et al., 2003) while one study, which did not differentiate between patients with PMR and GCA, found an increase. (Uddhammar et al., 2002)

In chapter 6 primary care data shows that patients with PMR appear to be less healthy, defined as a greater proportion of them have been diagnosed with one or more comorbid condition, than matched patients without PMR. However existing studies, although small, estimate that patients with PMR may actually have a reduced mortality rate compared to patients without the condition. By using linked mortality data produced by the Office for National Statistics, an answer to the question of the effect that PMR has on mortality will be produced.

7.2 Methods

7.2.1 Patient sample

Patients included in this study were identified from the case control and cohort CPRD analyses described in chapter 6. All patients from those analyses who were registered with a practice for which linkage was established to either the HES or ONS mortality datasets were included. As data linkage has only been established for practices in England, patients from practices in Northern Ireland, Scotland and Wales were not included in this analysis.

The patient sample used for this study was taken from the study described in chapter 6. The sample was already matched by age, sex and registered practice. As data linkage availability is defined by practice, equal proportions of cases and controls, who were similar in age and sex, were included in this study. Therefore, cases and controls should remain similar according to matching criteria, however to ensure this is the case, demographic information, including sex, age, and region will be tabulated.

Linkage between the HES and ONS datasets and the CPRD was established at different times, and the last date of data collection was also different for each linked dataset. Therefore, the number of cases and controls included, as well as the amount of time they contributed, was different in the HES and ONS mortality analyses. This will be explained in more detail in sections 7.2.2 and 7.2.6.

7.2.2 Hospital admissions

The first part of the analysis looked at rate of hospital admissions after index date. For cases, the index date was the date of diagnosis with PMR, for controls it was the date that their matched case was diagnosed. HES Admitted Patient Care data contains details of all admissions and attendances at English NHS healthcare providers. All NHS healthcare providers in England, including acute hospitals, primary care trusts and mental health trusts provide data contribute to this database. Augmented care data, including intensive care or high dependency units is also available. (CPRD, 2019)

A large number of domains of information are provided, (Dedman and Murray-Thomas, 2018) the domains of information relevant to this study are tabulated below (table 7-1).

Table 7-1: HES linked dataset domains

Domain	**Descriptors**
spno	Spell number uniquely identifying a hospitalisation
admidate	Date of admission
discharged	Date of discharge
admimeth	Method of admission
duration	Duration of hospitalisation (days)

The spell number provides a unique identification for each hospitalisation, while the admission and discharge dates ensure chronology of admissions can be established and also allow corroboration of the duration date provided in the HES dataset. The method of admission pertains to the setting that a patient has been admitted from. This is important to define who has referred the patient, where

from, and with what degree of urgency. The different types of admission code and definitions are tabulated below (table 7-2).

Table 7-2: Admission method codes and descriptions

Code	Description
Elective admission, when the decision to admit could be separated in time from the actual admission	
11	Waiting list
12	Booked
13	Planned
Emergency Admission, when admission is unpredictable and at short notice because of clinical need:	
21*	Accident and emergency or dental casualty department of the Health Care Provider
22*	GENERAL PRACTITIONER: after a request for immediate admission has been made direct to a Hospital Provider, i.e. not through a Bed bureau, by a GENERAL PRACTITIONER or deputy
23*	Bed bureau
24*	Consultant Clinic, of this or another Health Care Provider
25*	Admission via Mental Health Crisis Resolution Team
2A*	Accident and Emergency Department of another provider where the PATIENT had not been admitted
2B*	Transfer of an admitted PATIENT from another Hospital Provider in an emergency
2C	Baby born at home as intended
2D*	Other emergency admission
28*	Other means
Maternity Admission, except when the intention is to terminate the pregnancy	
31	Admitted ante-partum
32	Admitted post-partum
Other Admission not specified above	
82	The birth of a baby in this Health Care Provider
83	Baby born outside the Health Care Provider except when born at home as intended.
81	Transfer of any admitted PATIENT from other Hospital Provider other than in an emergency
	(NHS Digital, 2018)
* Included in the hospital admissions analysis	

For the analysis of number of hospital admissions, elective admissions were not included. Therefore, patients undergoing planned operations or regular dialysis

were excluded from the study and only those that were coded as emergency admissions were included. The codes, and therefore admissions, which were included are starred in the table above.

For the later study, of admissions due to a comorbidity, (section 7.2.3) all admissions, both elective and emergency, were included.

The time at which patients were at risk of admission during this study was the difference between the study start and end dates. These dates were calculated individually per patient. The study start date was defined as the index date. As the study sample was based on the one described in chapter 6, it included patients admitted from 1990 onwards. However, any cases diagnosed prior to April 1997, the date at which HES data collection began, were excluded because HES data was not available for some of their time at risk.

Data collection ended at the earliest of five events: 1) December 2017 (the final date of HES data collection) 2) the date when a patient transferred out of their HES/CPRD contributing practice, 3) the date of death, or 4) the last date of data collection from the practice. The aim of the study was to find the total number and rate of admissions, therefore patients were allowed to have multiple admissions and remain in the study until the end of data collection for that patient.

Therefore, at any specified time-point following index date, a patient could be classified as being in one of four states, that of:

1) Being at risk of admission (n=0)
2) Being admitted (n=1)
3) Being at risk of further admissions (n≥1)

4) Having previously been lost to follow up (censored)

In some cases, a patient may have more than one record of admission per hospitalisation, as defined by spell number. This could be due to failed discharges or erroneous recording of admission and discharge dates. Previous studies of hospital admissions using HES data reported the first admission in a treatment spell. (Anselmi et al., 2017; Han et al., 2017) This is therefore the approach that was taken in this study.

This process used is described in detail below. Three figures will be used to explain different permutations of admission dates. For example, in figure 7-1, there are two consecutive records for a single patient that were both acceptable for this study. In these, the discharge date of the first admission is before the admission date of the second.

Figure 7-1: Data management of admissions data (1)

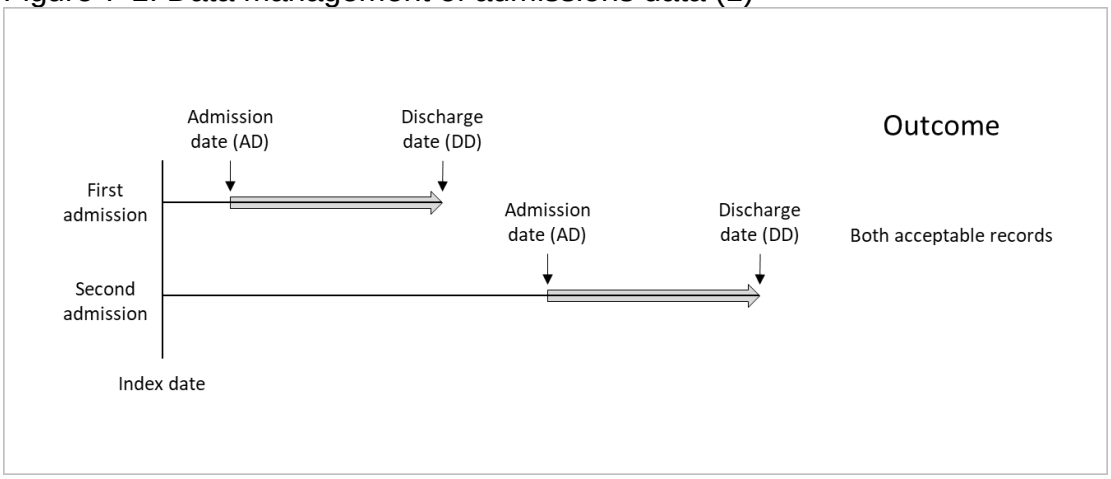


Figure 7-2 shows a different situation in which two consecutive records have the same admission date in the same treatment spell. In this case, if the discharge date for the second admission was the same or earlier than the first record, then

the second admission (and any further admissions in that spell) was removed. If the discharge date for the second admission date was later than the first admission, then the first discharge date was amended to the later date, and the second admission was then removed. In this scenario it is possible that either the patient mistakenly had two admissions recorded or that they were transferred during their admission.

Figure 7-2: Data management of admissions data (2)

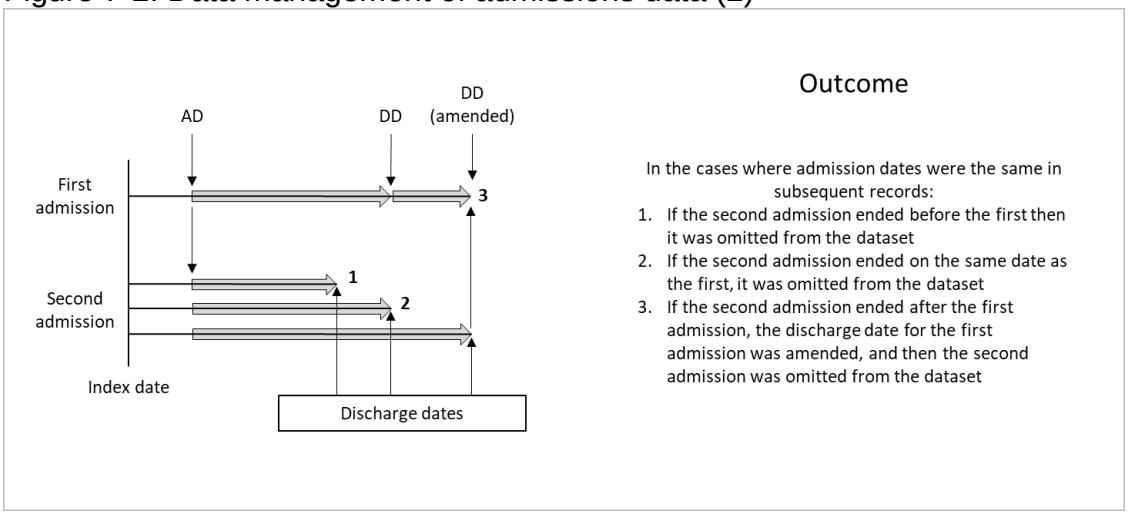
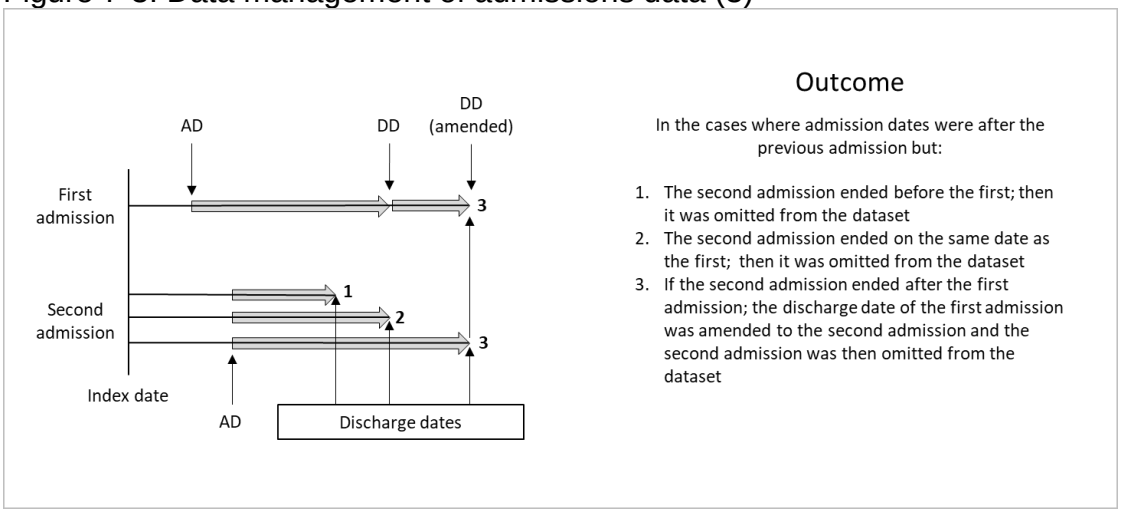


Figure 7-3 describes where two admissions for the same treatment spell fell within the same time period. In this case, the second admission date is after the first admission date, but before the first discharge date.

Figure 7-3: Data management of admissions data (3)



Here, similar to figure 7-2, if the second discharge date was either before or the same as the first discharge date then the second admission was removed from the dataset. If the second discharge date was later then the first discharge date, then the first discharge date was changed to reflect the second record's later date and then the second admission was removed.

As a result of this, the duration of some admissions changed and therefore the duration of each amended admission was recalculated using the new discharge dates.

7.2.3 Comorbidities

The second part of the analysis looked at the reasons for hospital admissions before, and after, index date. HES, as discussed earlier, provides information on multiple domains. Hospital based healthcare professionals routinely complete summaries of admissions to send to the patient's General Practitioner (GP),

which include the primary reason for admission, procedures carried out and a list of past medical history for each patient. These provide valuable information to GPs and Consultants alike. The aim of this study is to ascertain which comorbidities have led to hospital admissions. As discussed previously, unlike in the hospital admissions study, (section 7.2.2) both emergency and elective admissions were included for this analysis.

The comorbidities of interest in this study were the same comorbidities that were tested in the previous study (chapter 6) and the rationale for the choice of each comorbidity has already discussed in detail in a previous chapter (6.2.7). However, the coding system in HES is different to that used in CPRD. In CPRD, as previous discussed, diagnoses are based on Read codes. However, in HES the coding system used is ICD-10. In order to ensure access to robust and authenticated code lists to verify reasons for hospital admission, NHS digital publish a freely available, with permission, list of ICD-10 codes with diagnoses via the NHS Technology Reference Data Update Distribution (TRUD) service. (NHS Digital, 2015) It is this list that was used to identify comorbidities in this study. The ICD-10 codes that were included are listed in appendix 7.

7.2.4 Case control

The case control study assessed the proportion of cases and controls who had a hospital admission prior to index date with a comorbidity of interest. The time at which patients are at risk of admission during this study was the difference between the study start and end dates. Patients were included in the study after

the latest of four events: 1) the study start date 1st April 1997 (this is the date that HES data begins), 2) the date at which they became 40 years old, 3) the date they registered at a participating practice plus six months, or 4) the date at which the practice was adjudged to reach internal quality standards; known as the 'up-to-standard date'. Data collection ended at index date. The study sample was the same as in the admissions study described in (7.2.2) as all those with an index date prior to the study start date were again excluded.

The prevalence of hospital admission with a primary diagnosis of either one of the stratified or composite comorbidities were calculated prior to index date. Prevalence was calculated by dividing the total number of people with an admission for which the primary diagnosis was one of the comorbidities of interest (numerator) by the number of patients with PMR, or their controls (denominator). Furthermore, using the same methodology as the case control study in chapter 6, the likelihood of admission was described. The likelihood of admission was expressed as an odds ratio calculated using conditional logistic regression and were adjusted for smoking status, alcohol consumption and BMI category.

7.2.5 Cohort

The cohort study assessed a number of different measures of the likelihood of admission with a comorbidity in cases compared to controls, including the total number of admissions, the rate of admission due to each comorbidity per 10,000 person years and the likelihood of admission due to a comorbidity, which was

expressed as a hazard ratio. These ratios were adjusted for smoking status, alcohol consumption and BMI category as well as age and sex. For all of these calculations, patients with a record of admission due to that comorbidity prior to index date were excluded from the analysis.

The start and end date of the study were calculated individually for each patient. The start date was defined as the same as index date. The index date was either the date of diagnosis with PMR (cases) or, in the case of controls, the date of diagnosis of their matched case. Data collection ended at the earliest of five events: 1) 1st December 2017 (end of the period of time that HES encompasses), 2) the date when a patient transferred out of a practice, 3) the date of death, 4) the last date of data collection from the practice, or 5) the date of admission with the specified comorbidity. The study sample was the same as in the admissions study (7.2.2).

Similar to the cohort study in chapter 6, there was no minimum requirement for follow up following index date. Due to this, some patients were lost to follow up before they developed a comorbidity. These patients contributed data until the point at which they left the study.

Therefore, at any specified time-point following index date, a patient could be classified as being in one of three states, that of:

1) Having developed the event of interest
2) Being at risk of the event of interest
3) Having previously been lost to follow up (censored)

Again, using the same methods employed in chapter 6, the hazard ratio of admission due to each comorbidity was calculated using Cox proportional hazards and reported with 95% confidence intervals.

7.2.6 Mortality analysis

The final analysis was to ascertain whether differences in rates of comorbid diseases or hospital admissions, translated into changes in mortality. In order to provide estimates of mortality rates among patients with PMR and matched controls, the Office for National Statistics Death Registration database was used. This database is also linked to CPRD. The same patient sample as in Chapter 6 was used. The start of this study was defined as the index date which, as discussed previously, was the date of diagnosis of PMR for the case and their matched controls. Follow up continued until the earliest of several events: 1) 1st January 2018 (the end of the period of time that ONS Death Registration data encompasses), 2) the date when a patient transferred out of a practice, 3) the last date of data collection from the practice, or 4) the date of death.

The primary outcome measures were total number of deaths in cases and control groups, as well as mortality rate per 1,000 person years. Estimates of survival were also constructed using Kaplan-Meier methods. As these were time to event analyses and mortality data is only available from January 1998, all cases, and their matched controls, with diagnoses made prior to this date were excluded from the analysis. ONS Death Registration data includes the date of death and the date the death was registered. For this study the date of death was used.

A Poisson regression model, as described in chapter 3.2.3, was used to compare the mortality rate of PMR compared to controls, by calculating mortality rate ratios (IRR) with 95% confidence intervals.

Secondary outcome measures assessed included the cause of death. During registration of death in the United Kingdom, the certifying physician has to record the cause of death. This information may or may not be augmented by the results of a post-mortem examination of the body. Information about the cause of death is included within ONS Death Registration data. The primary cause of death was also tabulated by cases and controls. The cause of death, similar to HES data, is coded using the ICD-10 classification system. In the ONS dataset however, unlike HES, the description of a code is also included. Therefore there is no necessity to use a code list in order to describe this information.

7.2.7 Statistical analysis

Descriptive statistics were used to find average age of cases and controls as well as proportion of cases and controls per region, sex, smoking status, BMI category, alcohol consumption as well as follow up prior to, or following, index date as appropriate. These calculations were performed to ensure that cases and controls remain similar after removing patients who were registered with unlinked practices. The study demographics were checked on three occasions, once for all patients with linkage eligibility, once for patients contributing data to analyses of hospital admissions (including the case control and cohort studies) and once for patients contributing to the mortality analysis.

Regarding hospital admissions, the total number, and the rate of admissions for cases and controls was calculated. The number of admissions during the study period was the numerator and total follow up was the denominator. The rate was expressed per 1,000 person years. The hazard ratio with 95% confidence intervals, was calculated using Cox proportional hazards model.

The mean duration of each admission by case was calculated. This data was also categorised and presented as proportions of admissions lasting up to and including 0, 1, 3, 7, 14, 30 and 90 days. The total number of admissions per time period following index date was calculated. These time periods were within 1, 1-3, 3-6, and 6-12 months following index date. This reflects previous studies using the HES dataset, which also examined the period up until 12 months after index date, for example following an admission due to heart failure. (Bottle et al., 2016) Finally, Kaplan Meier methods were used to demonstrate time to first admission in cases and controls.

Some of the comorbidities included in the analysis, had very few admissions. In these cases, in order to protect patient anonymity, the prevalence or probability was censored and expressed as “<5”. Also, in these cases, measures of likelihood, either odds or hazard ratios were not calculated as there was insufficient power to generate meaningful results.

7.3 Results

7.3.1 Study demographics

A total of 181,420 matched patients were initially included in the study. Of these, 113,034 (62.3%) were registered at a practice which was linked to secondary care and ONS datasets and therefore eligible for these analyses. Of the patients who were excluded a similar proportion were cases and controls (table 7-3).

Table 7-3: Number of patients removed from study without linkage

	Case	**Control**	**Total**
Retained	20,083 (62.8%)	92,951 (62.2%)	113,034 (62.3%)
Not included in the study	11,901 (37.2%)	56,485 (37.8%)	68,386 (37.7%)

Demographic data for the remaining patients, including mean age at index date, sex, region of GP practice, smoking status, BMI category and alcohol consumption is presented in table 7-4. Follow up time is not presented here as it differs depending on which linked database was used (HES or ONS).

Table 7-4: Demographic information for comorbidities study

Variable	Total	Case	Control
Age			
Mean (SD)	73.5 (8.9)	73.8 (9.0)	73.5 (8.8)
Min/max	43.0 / 99.8	43.2 / 99.8	43.0 / 99.8
Sex (%)			
Male	36,484 (32.3)	6,627 (33.0)	29,857 (32.1)
Female	76,550 (67.7)	13,456 (67.0)	63,094 (67.9)
Region (%)			
North East	1,816 (1.6)	318 (1.6)	1,498 (1.6)
North West	14,437 (12.8)	2,542 (12.7)	11,895 (12.8)
Yorkshire & the Humber	4,060 (3.6)	728 (3.6)	3,332 (3.6)
East Midlands	3,071 (2.7)	537 (2.7)	2,534 (2.7)
West Midlands	15,978 (14.1)	2,776 (13.8)	13,202 (14.2)
East of England	16,546 (14.6)	2,896 (14.4)	13,650 (14.7)
South West	17,806 (15.8)	3,169 (15.8)	14,637 (15.7)
South Central	14,655 (13.0)	2,623 (13.1)	12,032 (12.9)
London	8,168 (7.2)	1,541 (7.7)	6,627 (7.1)
South East Coast	16,497 (14.6)	2,953 (14.7)	13,544 (14.6)
BMI category			
Normal(18.5-24.9)	36,347 (32.2)	6,412 (31.9)	29,935 (32.2)
Underweight (<18.5)	2,065 (1.8)	234 (1.2)	1,831 (2.0)
Overweight (25-29.9)	38,101 (33.7)	7,247 (36.1)	30,854 (33.2)
Obese (>=30)	22,128 (19.6)	4,235 (21.1)	17,893 (19.2)
Missing	14,393 (12.7)	1,955 (9.7)	12,438 (13.4)
Smoking			
Non-smoker	94,164 (83.3)	17,359 (86.4)	76,805 (82.6)
Smoker	12,714 (11.2)	2,003 (10.0)	10,711 (11.5)
Missing	6,156 (5.4)	721 (3.6)	5,435 (5.8)
Alcohol			
Never / no current	22,638 (20.0)	3,978 (19.8)	18,660 (20.1)
<10 units per week	58,406 (51.7)	10,873 (54.1)	47,533 (51.1)
10 or more units per week	16,764 (14.8)	3,062 (15.2)	13,702 (14.7)
Missing	15,226 (13.5)	2,170 (10.8)	13,056 (14.0)

The average age at diagnosis, sex and region of GP practice were very similar between cases and controls, reflecting the matching criteria that were applied. Cases were slightly older than controls, by an average of 0.3 years.

The three disease risk modifiers, BMI, smoking and alcohol consumption, were broadly similar between cases and controls. Data was less likely to be missing in

cases compared to controls, for example 13.4% of controls had no BMI recorded compared to 9.7% of cases. Cases were less likely to smoke (86.4% compared to 82.6%, and more likely to drink nothing or fewer than 10 units per week (73.9% compared to 71.1%), however they were more likely to be recorded as overweight or obese.

7.3.2 Hospital admissions

Following removal of patients where the index date was prior to the commencement of the HES database linkage, a total of 108,208 patients remained for analysis. Table 7-5 shows the proportion of excluded patients by case type.

Table 7-5: Number of patients removed from study as index date prior to study start date (HES)

	Case	**Control**	**Total**
Retained	19,197 (95.59%)	89,011 (95.76%)	108,208 (95.73%)
Not included in the study	886 (4.41%)	3,940 (4.24%)	4,826 (4.27%)

The proportion of patients excluded was small - less than 5% of linkage eligible records. A very similar proportion of cases and controls were excluded. The demographic information of patients included in the hospital admissions analyses are described in table 7-6. In addition to the previous table (7-4), the average time at risk contributed by cases and controls is also included. As this patient sample will be used in the hospital admissions, case control and cohort studies, time at risk before and after index date is shown.

Table 7-6: Demographic details Hospital admissions

Domain	Case	Control	Total
Mean age (SD)	73.8 (9.1)	73.5 (8.8)	73.6 (8.9)
Sex (%)			
Male	6,365 (33.2)	28,707 (32.3)	35,072 (32.4)
Female	12,832 (66.8)	60,304 (67.7)	73,136 (67.6)
Region (%)			
North East	308 (1.6)	1,443 (1.6)	1,751 (1.6)
North West	2,406 (12.5)	11,262 (12.7)	13,668 (12.6)
Yorkshire & the Humber	655 (3.4)	3,010 (3.4)	3,665 (3.4)
East Midlands	505 (2.6)	2,386 (2.7)	2,891 (2.7)
West Midlands	2,652 (13.8)	12,630 (14.2)	15,282 (14.1)
East of England	2,712 (14.1)	12,821 (14.4)	15,533 (14.4)
South West	3,062 (16.0)	14,183 (15.9)	17,245 (15.9)
South Central	2,559 (13.3)	11,760 (13.2)	14,319 (13.2)
London	1,480 (7.7)	6,381 (7.2)	7,861 (7.3)
South East Coast	2,858 (14.9)	13,135 (14.8)	15,993 (14.8)
Total time at risk (years)			
Mean (SD)	18.4 (2.8)	18.1 (3.1)	18.2 (3.1)
Pre-index date time at risk (years)			
Mean (SD)	8.6 (4.3)	8.2 (4.2)	8.3 (4.2)
Post-index date time at risk (years)			
Mean (SD)	9.9 (4.6)	9.9 (4.6)	9.9 (4.6)
BMI category			
Normal (18.5-24.9)	6,132 (31.9)	28,896 (32.5)	35,028 (32.4)
Underweight (<18.5)	222 (1.2)	1,781 (2.0)	2,003 (1.9)
Overweight (25-29.9)	7,004 (36.5)	29,911 (33.6)	36,915 (34.1)
Obese (>=30)	4,160 (21.7)	17,526 (19.7)	21,686 (20.0)
Missing	1,679 (8.7)	10,897 (12.2)	12,576 (11.6)
Smoking			
Non-smoker	16,761 (87.3)	74,346 (83.5)	91,107 (84.2)
Smoker	1,867 (9.7)	10,180 (11.4)	12,047 (11.1)
Missing	569 (3.0)	4,485 (5.0)	5,054 (4.7)
Alcohol			
Never / no current	3,828 (19.9)	17,994 (20.2)	21,822 (20.2)
<10 units per week	10,486 (54.6)	46,076 (51.8)	56,562 (52.3)
10 or more units per week	2,973 (15.5)	13,339 (15.0)	16,312 (15.1)
Missing	1,910 (9.9)	11,602 (13.0)	13,512 (12.5)

The demographic details in this sample of linked patients are similar to the larger sample containing all the patients with data linkage. This is to be expected given less than 5% of the patients, and a similar proportion of cases and controls, were excluded from this analysis.

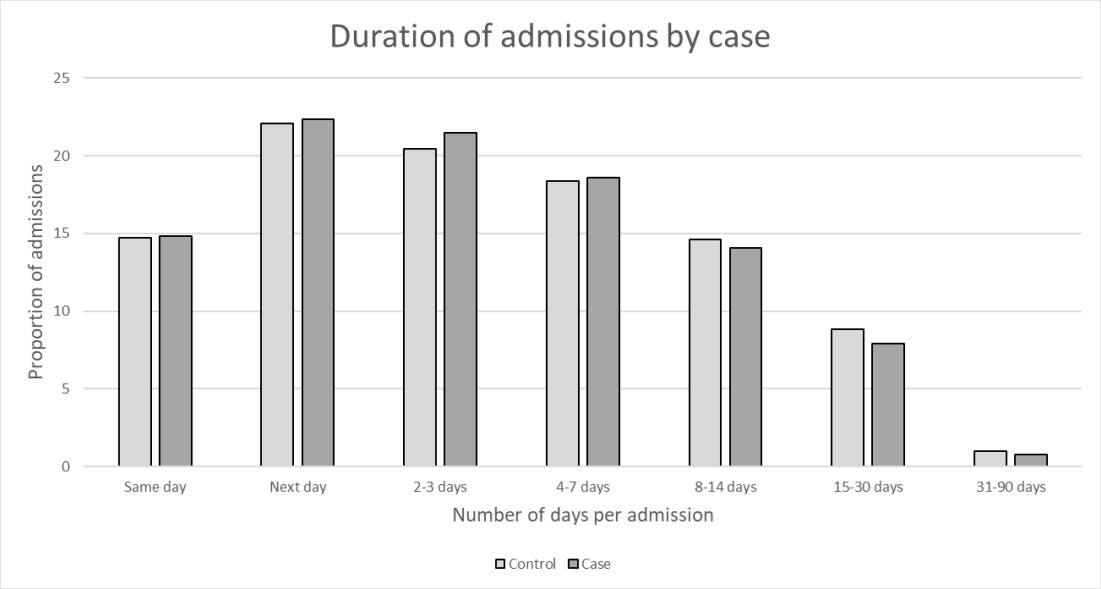
Having satisfied the precondition that the cases and controls are similar, descriptive statistics relating to admissions, including number with at least one admission, the overall rate of admissions and the duration of admissions is tabulated below (table 7-7).

Table 7-7: Admission rates following index date

	Cases	**Controls**	**Total**
Number who have at least one admission (%)			
	12,783 (66.6)	51,832 (58.23)	64,615 (59.7)
Admission rate per 1,000 person years (95% CI)			
	235.05 (232.88,237.24)	173.45 (172.58,174.32)	184.34 (183.53,185.15)
Hazard ratio		1.18 (1.17, 1.19)	
Duration of admissions			
Median (IQR)	5 (1, 13)	5 (1, 12)	5 (1, 13)
Min / max	0.0 / 335.0	0.0 / 434.0	0.0 / 434.0
Mean (95% CI)	10.6 (10.4, 10.8)	11.4 (11.4, 11.5)	11.3 (11.2, 11.3)

The proportion of cases with at least one episode of hospitalisation is greater than controls (67% compared to 58%). Furthermore, the rate of admissions, per 1,000 person years is higher at 235.1 for cases, compared to 173.5 in controls. The hazard ratio shows that cases are around 18% more likely to be admitted to hospital compared to controls. However, it is noted that the average duration of admission was the same in cases and controls, with a median of 5 days for each. In order to better visualise the average length of stay, the duration of admissions are presented graphically in figure 7-4.

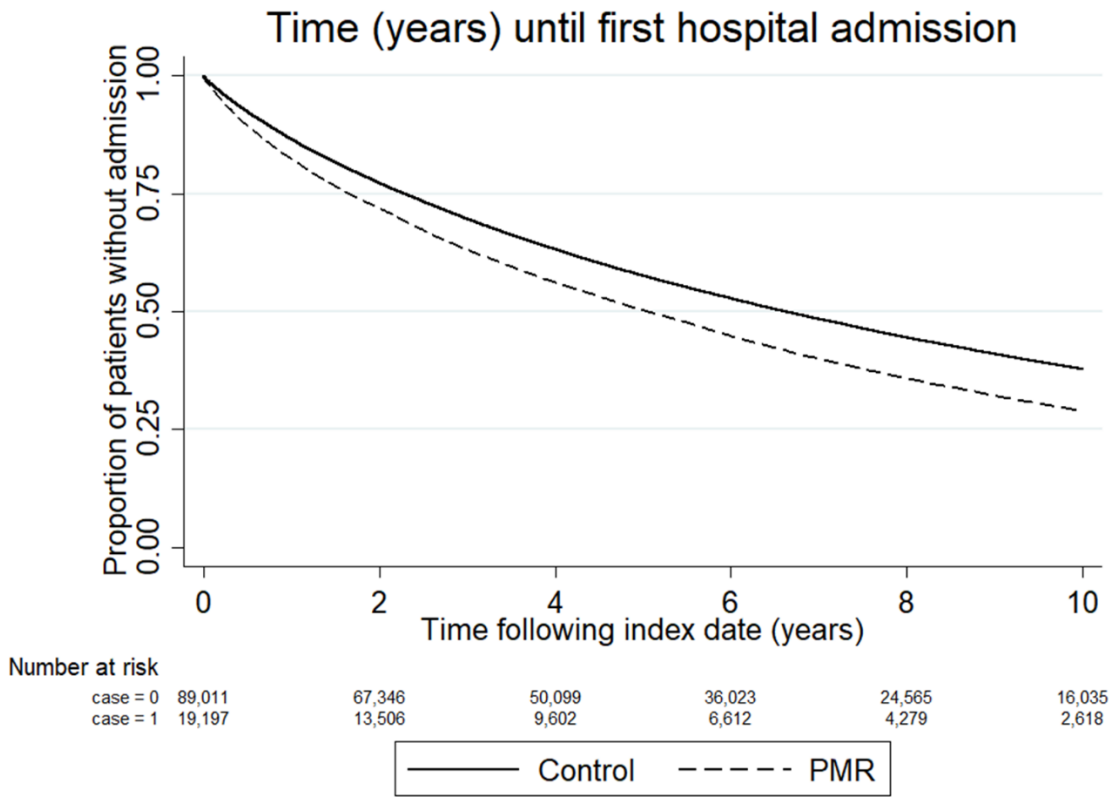
Figure 7-4: Duration of admission by case



It can be seen that a greater proportion of admissions for cases were of shorter duration (zero, 1, 2-3 or 4-7 days), while admissions of 8-14, 15-30 or 31-90 days were proportionally more likely in controls. This shows that, although patients with PMR were more likely to be admitted to hospital, their matched controls had on average longer admissions. The mean duration of admissions, with 95% confidence intervals was higher than the median values, at 10.6 days (10.4, 10.8) for cases and 11.4 days (11.4, 11.5) for controls.

To investigate further the effect that a diagnosis of PMR had on hospital admissions the time until first admission following index date is demonstrated using Kaplan-Meier analysis (figure 7-5).

Figure 7-5: Kaplan-Meier estimates of time to first admission by case



It can be seen that for the proportion of the patients with PMR, half have been admitted to hospital on at least one occasion five years after index date, while for controls this becomes the case more than six years after index date. The difference in likelihood of an admission persists over a ten year period after index date.

Finally, the number of admissions per categorised time period is described in table 7-8 and shown in figure 7-6. In order to preserve anonymity, if fewer than 5 admissions were recorded for cases or controls, or fewer than 10 overall, then this data is not presented.

Table 7-8: Absolute number and proportion admitted following index date

Number of admissions (%)			
	Case	**Control**	**Total**
Less than one month			
0	18,773 (97.8)	87,624 (98.4)	106,397 (98.3)
1	406 (2.1)	1,308 (1.5)	1,714 (1.6)
2	16 (0.1)	72 (0.1)	0,088 (0.1)
3	<5 (0.0)	7 (0.0)	<10 (0.0)
4	<5 (0.0)	<5 (0.0)	<10 (0.0)
5 +	<5 (0.0)	<5 (0.0)	<10 (0.0)
One to three months			
0	18,407 (95.9)	86,429 (97.1)	104,836 (96.9)
1	703 (3.7)	2,290 (2.6)	2,993 (2.8)
2	80 (0.4)	244 (0.3)	324 (0.3)
3	<5 (0.0)	41 (0.0)	46 (0.0)
4	<5 (0.0)	6 (0.0)	<10 (0.0)
5 +	<5 (0.0)	6 (0.0)	<10 (0.0)
Three to six months			
0	18,114 (94.4)	85,284 (95.8)	103,398 (95.6)
1	909 (4.7)	3,182 (3.6)	4,091 (3.8)
2	139 (0.7)	457 (0.5)	596 (0.6)
3	30 (0.2)	65 (0.1)	95 (0.1)
4	<5 (0.0)	16 (0.0)	20 (0.0)
5 +	<5 (0.0)	7 (0.0)	<10 (0.0)
Six to twelve months			
0	17,350 (90.4)	82,281 (92.4)	99,631 (92.1)
1	1,424 (7.4)	5,303 (6.0)	6,727 (6.2)
2	301 (1.6)	1,048 (1.2)	1,349 (1.2)
3	86 (0.4)	262 (0.3)	348 (0.3)
4	27 (0.1)	70 (0.1)	97 (0.1)
5 +	<5 (0.0)	47 (0.1)	56 (0.1)

The majority of patients do not have an admission in each time period, therefore figure 7-6 is scaled to 70-100% in order to better demonstrate any differences observed.

Figure 7-6: Number of admissions per time period

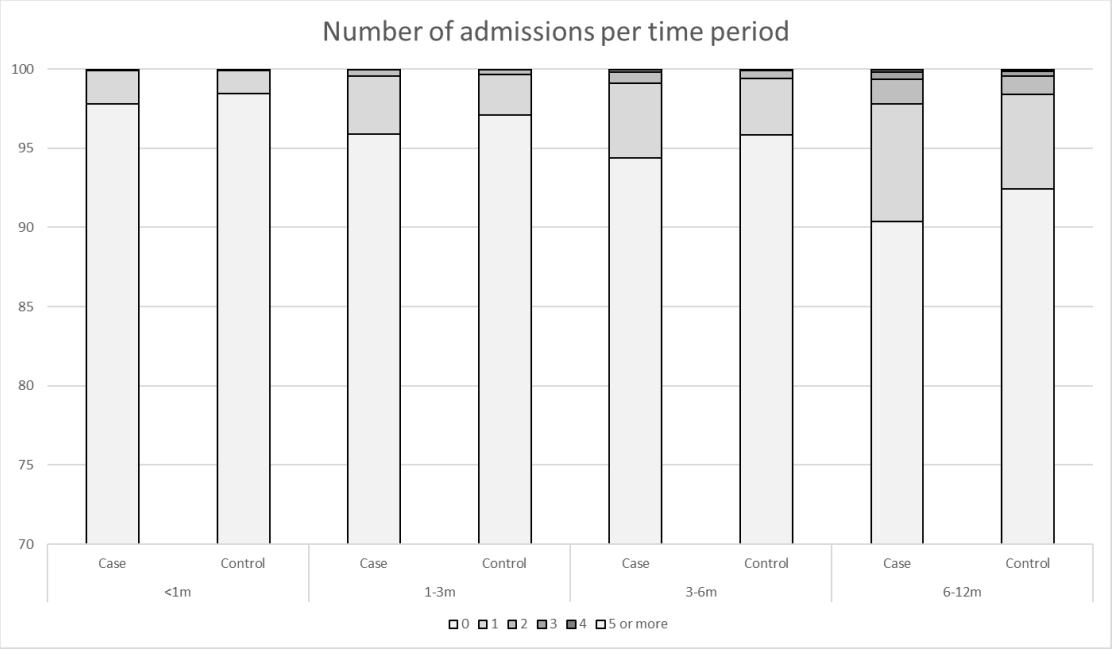


Table 7-8 and figure 7-6 demonstrate that at all time periods controls were less likely to have been admitted and cases were more likely to have multiple admissions.

7.3.3 Case control study

Due to the large number of outcomes reported in this study a number of abbreviations have been used in the tables. The abbreviations are shown in table 7-9.

Table 7-9: Abbreviations for comorbid outcomes

Comorbidity	Abbreviation
Leukaemia, lymphoma	LL
Cardiovascular disease	CVD
Congestive cardiac failure	CCF
Peripheral vascular disease	PVD
Cerebrovascular disease	CVA
Hypertension	HTN
Chronic obstructive pulmonary disease	COPD
Ulcerative colitis	UC
Systemic lupus erythematosus	SLE
Rheumatoid arthritis	RA
Osteoarthritis	OA
Type 1 Diabetes mellitus	T1DM
Type 2 Diabetes mellitus	T2DM
Multiple sclerosis	MS
Urinary tract infection	UTI
Upper respiratory tract infection	URTI
Lower respiratory tract infection	LRTI

The first part of the analysis of comorbidities, prior to index date, was to look at the prevalence of admission to hospital with one of the composite outcomes prior to index date. These are summarised in table 7-10.

Table 7-10: Prevalence of composite comorbidities prior to index date

	Case (%)	Control (%)
Cancer	1,191 (6.2)	6,462 (7.3)
Vascular	1,924 (10.0)	8,298 (9.3)
Respiratory	374 (1.9)	1,522 (1.7)
Gastroenterological	1,755 (9.1)	6,140 (6.9)
Immunological	320 (1.7)	457 (0.5)
Endocrine	153 (0.8)	762 (0.9)
Neurological	21 (0.1)	415 (0.6)
Psychiatric	77 (0.4)	538 (0.6)
Ophthalmological	2,238 (11.7)	8,759 (9.8)
Infections	851 (4.4)	3,683 (4.1)
Fragility fractures	332 (1.7)	2,326 (2.6)

A smaller proportion of cases were admitted with a neoplastic, neurological, endocrine, psychiatric, ophthalmic or infectious disease compared to controls. However a higher proportion of cases were admitted with vascular, respiratory, gastroenterological, immunological conditions and fragility fractures.

In order to gain a better understanding of the detail of what conditions contribute most to the composite outcomes, table 7-11 shows the conditions stratified into individual comorbidities.

A similar pattern to the composite comorbidities was seen when outcomes are stratified. Admissions due to neoplastic, neurological, psychiatric and endocrine conditions were either as common or more common in controls compared to cases. Similarly, most admissions due to vascular, respiratory or gastroenterological diseases were more common in cases.

It is observed in many of the categories the number of admissions was under five, even among controls. In these cases, to preserve anonymity, the exact number recorded was censored.

Table 7-11: Prevalence of admission with stratified comorbidities prior to index date

	Cases (%)	Controls (%)
Cancer		
Breast cancer	222 (1.2)	1,231 (1.4)
Prostate cancer	118 (0.6)	557 (0.6)
Lung cancer	20 (0.1)	217 (0.2)
Colon cancer	150 (0.8)	847 (1.0)
Melanoma	30 (0.2)	188 (0.2)
LL	39 (0.2)	332 (0.4)
Vascular		
CVD	441 (2.3)	1,849 (2.1)
CCF	191 (1.0)	952 (1.1)
PVD	192 (1.0)	809 (0.9)
CVA	309 (1.6)	1,778 (2.0)
HTN	49 (0.3)	329 (0.4)
Respiratory		
Asthma	124 (0.6)	314 (0.4)
COPD	208 (1.1)	0,996 (1.1)
Lung fibrosis	19 (0.1)	103 (0.1)
Renal		
Renal disease	23 (0.1)	180 (0.2)
Gastroenterological		
Liver disease	33 (0.2)	158 (0.2)
Peptic ulcers	1,650 (8.6)	5,760 (6.5)
Crohn's disease	30 (0.2)	91 (0.1)
Ulcerative colitis	65 (0.3)	232 (0.3)
Autoimmune and musculoskeletal		
SLE	<5 (0.0)	13 (0.0)
Systemic sclerosis	<5 (0.0)	<5 (0.0)
Rheumatoid arthritis	52 (0.3)	349 (0.4)
Sjogren’s syndrome	<5 (0.0)	<5 (0.0)
Psoriatic arthritis	<5 (0.0)	<5 (0.0)
Raynaud's disease	<5 (0.0)	<5 (0.0)
Osteoarthritis	1,881 (9.8)	6,952 (7.8)
Endocrine		
Hyperthyroidism	9 (0.0)	50 (0.1)
Hypothyroidism	7 (0.0)	23 (0.0)
T1DM	18 (0.1)	129 (0.2)
T2DM	52 (0.3)	304 (0.3)
Neurological and psychiatric		
Dementia	6 (0.0)	232 (0.3)
Parkinson's disease	<5 (0.0)	87 (0.1)
MS	<5 (0.0)	46 (0.1)
Psychiatric		
Schizophrenia	<5 (0.0)	36 (0.1)
Bipolar disease	6 (0.0)	65 (0.1)
Depression	42 (0.2)	276 (0.3)

	Cases (%)	Controls (%)
Anxiety	26 (0.1)	157 (0.2)
Complications due to glucocorticoids		
Osteoporosis	43 (0.2)	184 (0.2)
Hip fracture	197 (1.0)	1,446 (1.6)
Wrist fracture	126 (0.7)	846 (1.0)
Vertebral fracture	<5 (0.0)	<5 (0.0)
Ophthalmological		
Cataracts	2,166 (11.3)	8,534 (9.6)
Glaucoma	124 (0.6)	390 (0.4)
Infections		
UTI	92 (0.5)	376 (0.4)
URTI	43 (0.2)	123 (0.1)
LRTI	520 (2.7)	2,209 (2.5)
Skin infections	227 (1.2)	1,095 (1.2)

Abbreviations: Leukaemia, lymphoma (LL), Cardiovascular disease (CVD), Congestive cardiac failure (CCF), Peripheral vascular disease (PVD), Cerebrovascular disease (CVA), Hypertension (HTN), Chronic obstructive pulmonary disease (COPD), Ulcerative colitis (UC), Systemic Lupus Erythematosus (SLE), rheumatoid arthritis (RA), Osteoarthritis (OA), Type 1 Diabetes mellitus (T1DM), Type 2 Diabetes mellitus (T2DM), Multiple sclerosis (MS), Urinary tract infection (UTI), Upper respiratory tract infection (URTI), Lower respiratory tract infection (LRTI)

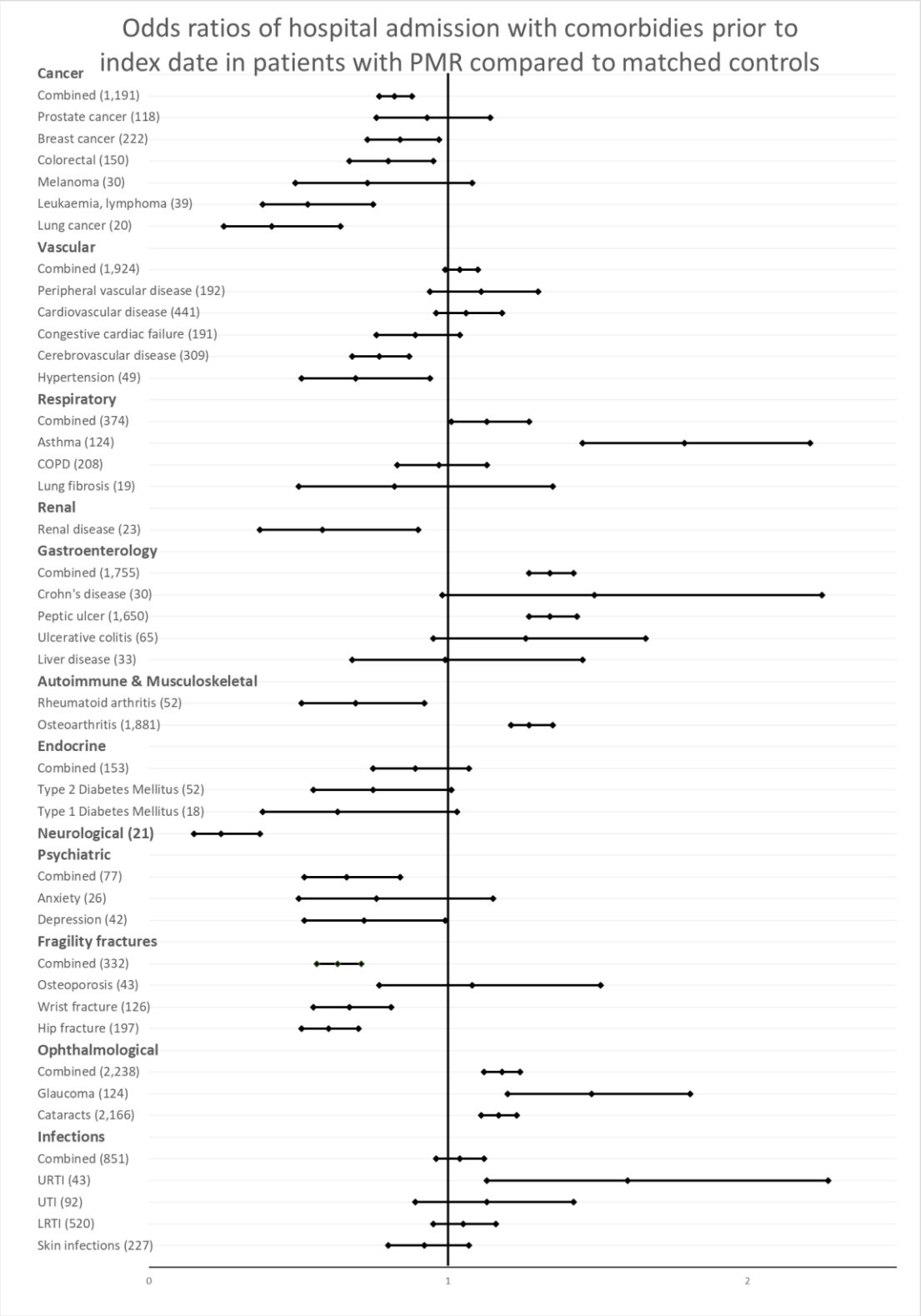
Whether the observed differences in prevalence of admissions were statistically significant is now estimated. Conditional logistic regression was used to calculate odd ratios with 95% confidence intervals. There were, however, a number of stratified comorbidities in which an insufficient number of admissions were recorded to generate accurate estimates. In these cases, therefore, odds ratios were not calculated. The conditions for which odds ratios were not calculated included: SLE, systemic sclerosis, Sjogren's syndrome, psoriatic arthritis, Raynaud's disease, thyroid disease, dementia, Parkinson's disease, MS, schizophrenia and bipolar disease. The odds ratios are tabulated below (table 7-12) and graphically illustrated also (figure 7-7). The odds ratio of a pre-existing admission due to any immunological disease was particularly high (3.27, [2.83, 3.79]), therefore this was not included in the forest plot (figure 7-7) in order to allow better visualisation of the other outcomes.

Table 7-12: Odds ratios PMR vs controls of admission due to a comorbidity prior to index date

Comorbidity	OR (95% CI)	Comorbidity	OR (95% CI)
Cancer	0.82 (0.77,0.88)	**Immunological**	3.27 (2.83,3.79)
Breast cancer	0.84 (0.73,0.97)	Rheumatoid arthritis	0.69 (0.51,0.92)
Prostate cancer	0.93 (0.76,1.14)	Osteoarthritis	1.27 (1.21,1.35)
Lung cancer	0.41 (0.25,0.64)	**Endocrine**	0.89 (0.75,1.07)
Colon cancer	0.80 (0.67,0.95)	T1DM	0.63 (0.38,1.03)
Melanoma	0.73 (0.49,1.08)	T2DM	0.75 (0.55,1.01)
Leukaemia, lymphoma	0.53 (0.38,0.75)	**Neurological**	0.24 (0.15,0.37)
Vascular	1.04 (0.99,1.10)	**Psychiatric**	0.66 (0.52,0.84)
CVD	1.06 (0.96,1.18)	Depression	0.72 (0.52,0.99)
CCF	0.89 (0.76,1.04)	Anxiety	0.76 (0.50,1.15)
PVD	1.11 (0.94,1.30)	**Fragility fractures**	0.63 (0.56,0.71)
CVA	0.77 (0.68,0.87)	Osteoporosis	1.08 (0.77,1.51)
HTN	0.69 (0.51,0.94)	Hip fracture	0.60 (0.51,0.70)
Respiratory	1.13 (1.01,1.27)	Wrist fracture	0.67 (0.55,0.81)
Asthma	1.79 (1.45,2.21)	**Ophthalmological**	1.18 (1.12,1.24)
COPD	0.97 (0.83,1.13)	Cataracts	1.17 (1.11,1.23)
Lung fibrosis	0.82 (0.50,1.35)	Glaucoma	1.48 (1.20,1.81)
Gastroenterological	1.34 (1.27,1.42)	**Infections**	1.04 (0.96,1.12)
Moderate liver disease	0.99 (0.68,1.45)	UTI	1.13 (0.89,1.42)
Peptic ulcers	1.34 (1.27,1.43)	URTI	1.60 (1.13,2.27)
Crohn's disease	1.49 (0.98,2.25)	LRTI	1.05 (0.95,1.16)
Ulcerative colitis	1.26 (0.95,1.66)	Skin infections	0.92 (0.80,1.07)
Renal			
Renal disease	0.58 (0.37,0.90)		

Abbreviations: Odds Ratio (OR) Leukaemia, lymphoma (LL), Cardiovascular disease (CVD), Congestive cardiac failure (CCF), Peripheral vascular disease (PVD), Cerebrovascular disease (CVA), Hypertension (HTN), Chronic obstructive pulmonary disease (COPD), Ulcerative colitis (UC), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Osteoarthritis (OA), Type 1 Diabetes mellitus (T1DM), Type 2 Diabetes mellitus (T2DM), Multiple sclerosis (MS), Urinary tract infection (UTI), Upper respiratory tract infection (URTI), Lower respiratory tract infection (LRTI)

Figure 7-7: Odds ratios of admission with specified comorbidity in patients with PMR vs controls prior to index date



Only a small number of stratified or composite outcomes reached statistical significance. Of the composite outcomes, controls were significantly more likely to be admitted with neoplastic or psychiatric diseases and fragility fractures, while case were more likely to be admitted with gastroenterological and ophthalmological conditions. The increase in the risk of admissions in PMR in vascular and respiratory conditions was not statistically significant.

Regarding stratified outcomes, admissions with most of the different cancer types, including breast, colorectal, leukaemia and lymphoma as well as lung cancer are significantly less likely to have occurred in patients who went on to develop PMR. Alongside these outcomes, admissions due to cerebrovascular disease, hypertension and renal disease were also significantly less likely.

Conversely, patients with PMR are significantly more likely to have experienced an admission due to asthma, osteoarthritis, peptic ulcers, cataracts, glaucoma and upper respiratory tract infections.

7.3.4 Cohort study

The first part of the prospective analysis into admission due to comorbidities following index date was an assessment of the total number, proportion and rate of new admissions with composite comorbidities in cases and controls. Table 7-13 describes this.

Table 7-13: Total number, proportion and rate (per 10,000 person years) of new admissions with composite outcomes following index date

	Cases				Controls			
Comorbidity	**At risk**	**New admissions**	**%**	**Rate (95% CI)**	**At risk**	**New admissions**	**%**	**Rate (95% CI)**
Cancer	17,820	2,663	14.9	287.3 (276.6,298.4)	81,446	12,090	14.8	313.9 (308.4,319.6)
Vascular	16,915	3,639	21.5	422.8 (409.2,436.7)	79,195	12,873	16.3	348.6 (342.6,354.7)
Respiratory	18,781	928	4.9	96.1 (90.1,102.5)	87,294	3,185	3.6	78.9 (76.2,81.7)
Gastroenterological	18,810	411	2.2	42.6 (38.7,46.9)	87,411	1,538	1.8	38.2 (36.3,40.1)
Immunological	18,787	663	3.5	69.6 (64.5,75.1)	88,415	406	0.5	10.0 (9.0,11.0)
Endocrine	19,016	332	1.7	33.9 (30.5,37.8)	88,079	1,118	1.3	27.5 (25.9,29.2)
Neurological	19,170	340	1.8	34.3 (30.9,38.2)	88,472	2,010	2.3	49.0 (47.0,51.2)
Psychiatric	19,102	145	0.8	14.7 (12.5,17.3)	88,246	638	0.7	15.7 (14.5,16.9)
Ophthalmological	16,693	3,832	23.0	468.7 (454.1,483.7)	78,823	12,835	16.3	357.4 (351.2,363.6)
Infections	18,207	3,376	18.5	357.0 (345.1,369.2)	84,737	11,894	14.0	296.7 (291.4,302.0)
Fragility fractures	18,809	1,480	7.9	153.2 (145.6,161.3)	86,278	6,007	7.0	149.8 (146.1,153.7)

The rate of admission with any comorbidity following diagnosis is consistently higher in cases compared to controls, with the only exception being admissions with cancer and neurological diseases. The number of cases and controls varied with each composite outcome as any patients with a record of admission with one of the comorbidities prior to index date were excluded.

Table 7-14 describes the total number, proportion and rate of admissions due to one of the stratified outcomes by case. A number of the stratified comorbidities had fewer than ten recorded admissions. These included SLE, systemic sclerosis, Sjogren's disease, psoriatic arthritis, Raynaud's disease, hypothyroidism, MS, schizophrenia, bipolar affective disorder, and vertebral fracture. Where there were fewer than five admissions, these outcomes are displayed as <5 to preserve anonymity.

Table 7-14: Total number, proportion and rate (per 10,000 person years) of admissions with stratified outcomes after index date

	Cases				Controls			
	At risk	New admissions	%	Rate (95% CI)	At risk	New admissions	%	Rate (95% CI)
Cancer								
Breast cancer	18,931	224	1.2	22.6 (19.8,25.8)	87,488	1,296	1.5	31.5 (29.9,33.3)
Prostate cancer	19,066	179	0.9	18.2 (15.8,21.1)	88,387	839	0.9	20.6 (19.3,22.1)
Lung cancer	19,173	294	1.5	29.7 (26.5,33.3)	88,774	1,416	1.6	34.5 (32.8,36.4)
Colon cancer	19,022	351	1.8	35.9 (32.3,39.8)	88,023	1,563	1.8	38.5 (36.7,40.5)
Melanoma	19,165	66	0.3	6.7 (5.2,8.5)	88,792	324	0.4	7.9 (7.1,8.8)
Leukaemia, lymphoma	19,150	212	1.1	21.5 (18.8,24.6)	88,622	923	1.0	22.6 (21.2,24.1)
Vascular								
CVD	18,669	967	5.2	100.7 (94.6,107.3)	86,748	3,125	3.6	78.0 (75.3,80.7)
CCF	18,982	982	5.2	99.9 (93.9,106.4)	87,919	3,461	3.9	84.9 (82.1,87.8)
PVD	18,977	557	2.9	57.2 (52.6,62.1)	88,078	1,518	1.7	37.4 (35.5,39.3)
CVA	18,842	1,258	6.7	129.2 (122.2,136.5)	86,871	5,266	6.1	130.6 (127.1,134.1)
HTN	19,134	155	0.8	15.7 (13.5,18.4)	88,630	549	0.6	13.4 (12.4,14.6)
Respiratory								
Asthma	19,050	131	0.7	13.4 (11.3,15.9)	88,609	409	0.5	10.0 (9.1,11.0)
COPD	18,962	659	3.5	67.6 (62.6,72.9)	87,867	2,357	2.7	58.0 (55.7,60.4)
Lung fibrosis	19,180	116	0.6	11.7 (9.8,14.1)	88,954	319	0.4	7.8 (7.0,8.7)
Renal								
Renal disease	19,170	131	0.7	13.3 (11.2,15.7)	88,805	455	0.5	11.1 (10.1,12.2)
Gastroenterological								
Moderate liver disease	19,156	88	0.5	8.9 (7.2,11.0)	88,822	319	0.4	7.8 (7.0,8.7)
Peptic ulcers	18,962	258	1.4	26.5 (23.4,29.9)	87,997	1,064	1.2	26.3 (24.7,27.9)
Crohn's disease	19,155	28	0.1	2.8 (2.0,4.1)	88,885	58	0.1	1.4 (1.1,1.8)
Ulcerative colitis	19,118	56	0.3	5.7 (4.4,7.4)	88,698	170	0.2	4.2 (3.6,4.8)
Autoimmune and musculoskeletal								
SLE	19,193	7	N/A	N/A	88,994	6	N/A	N/A
Systemic sclerosis	19,196	<5	N/A	N/A	89,003	14	0.0	0.3 (0.2,0.6)
Rheumatoid arthritis	19,124	216	1.1	22.0 (19.3,25.2)	88,551	225	0.3	5.5 (4.8,6.3)
Sjogren’s syndrome	19,197	<5	N/A	N/A	89,011	<5	N/A	N/A
Psoriatic arthritis	19,197	<5	N/A	N/A	89,011	<5	N/A	N/A
Raynaud's disease	19,197	<5	N/A	N/A	89,011	<5	N/A	N/A
Osteoarthritis	16,981	2,532	14.9	295.2 (283.9,306.9)	80,592	7,141	8.9	193.2 (188.8,197.8)

	Cases				Controls			
	At risk	New admissions	%	Rate (95% CI)	At risk	New admissions	%	Rate (95% CI)
Endocrine								
Hyperthyroidism	19,185	12	0.1	1.2 (0.7,2.1)	88,944	49	0.1	1.2 (0.9,1.6)
Hypothyroidism	19,190	10	N/A	N/A	88,981	46	0.1	1.1 (0.8,1.5)
T1DM	19,175	26	0.1	2.6 (1.8,3.9)	88,842	89	0.1	2.2 (1.8,2.7)
T2DM	19,137	196	1.0	19.9 (17.3,22.9)	88,657	550	0.6	13.5 (12.4,14.6)
Neurological and psychiatric								
Dementia	19,189	247	1.3	24.9 (22.0,28.2)	88,697	1,593	1.8	38.8 (37.0,40.8)
Parkinson's disease	19,189	54	0.3	5.5 (4.2,7.1)	88,911	297	0.3	7.2 (6.5,8.1)
MS	19,195	9	N/A	N/A	88,940	31	0.0	0.8 (0.5,1.1)
Psychiatric								
Schizophrenia	19,196	<5	N/A	N/A	88,945	32	0.0	0.8 (0.6,1.1)
Bipolar disease	19,188	9	N/A	N/A	88,914	62	0.1	1.5 (1.2,1.9)
Depression	19,143	65	0.3	6.6 (5.2,8.4)	88,609	272	0.3	6.6 (5.9,7.5)
Anxiety	19,167	61	0.3	6.2 (4.8,7.9)	88,795	259	0.3	6.3 (5.6,7.2)
Complications due to glucocorticoids								
Osteoporosis	19,151	314	1.6	31.9 (28.6,35.6)	88,800	594	0.7	14.5 (13.4,15.7)
Hip fracture	18,975	1,150	6.1	117.7 (111.1,124.7)	87,306	4,918	5.6	121.1 (117.8,124.5)
Wrist fracture	19,040	293	1.5	29.9 (26.7,33.5)	88,000	1,189	1.4	29.4 (27.7,31.1)
Vertebral fracture	19,197	<5	N/A	N/A	89,011	<5	N/A	N/A
Ophthalmological								
Cataracts	16,770	3,808	22.7	463.0 (448.6,478.0)	79,099	12,730	16.1	353.0 (346.9,359.2)
Glaucoma	19,048	145	0.8	14.8 (12.6,17.4)	88,511	488	0.6	12.0 (11.0,13.1)
Infections								
UTI	19,092	111	0.6	11.3 (9.4,13.6)	88,565	453	0.5	11.1 (10.1,12.2)
URTI	19,149	59	0.3	6.0 (4.6,7.7)	88,857	195	0.2	4.8 (4.1,5.5)
LRTI	18,595	2,882	15.5	297.4 (286.8,308.5)	86,480	10,120	11.7	247.6 (242.8,252.5)
Skin infections	18,922	701	3.7	71.9 (66.7,77.4)	87,711	2,187	2.5	53.9 (51.7,56.3)

Abbreviations: Leukaemia, lymphoma (LL), Cardiovascular disease (CVD), Congestive cardiac failure (CCF), Peripheral vascular disease (PVD), Cerebrovascular disease (CVA), Hypertension (HTN), Chronic obstructive pulmonary disease (COPD), Ulcerative colitis (UC), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Osteoarthritis (OA), Type 1 Diabetes mellitus (T1DM), Type 2 Diabetes mellitus (T2DM), Multiple sclerosis (MS), Urinary tract infection (UTI), Upper respiratory tract infection (URTI), Lower respiratory tract infection (LRTI)

The number of comorbidities for which the risk of admission over the study period was greater than 1% was low. Comorbidities for which the risk of admission was greater than 1% included, breast, lung and colorectal cancer, leukaemia and lymphoma, asthma, COPD, pulmonary fibrosis, osteoarthritis, dementia, osteoporosis, hip and wrist fractures, cataracts, lower respiratory tract and skin infections, peptic ulcers and all vascular outcomes except hypertension. The rate of admission with neoplastic and neurological conditions was higher in controls compared to cases. The rate of admission with vascular, respiratory, gastroenterological, rheumatoid arthritis, osteoarthritis, endocrine, psychiatric, ophthalmological and infectious diseases was higher in cases. The rate of admission for hip fracture was higher in controls, however, the rate for wrist fracture was higher among cases.

Whether the differences in the risk of admission with each comorbidity was significant was investigated using Cox proportional hazards, to calculate hazard ratios (HR), the results of which are displayed in table 7-15. To ensure sufficient power, hazard ratios were only calculated where comorbidities had greater than 10 admissions following index date. Finally, to test the proportional hazards assumption, Kaplan-Meier estimates of time to first admission with each comorbidity were also produced graphically for each comorbidity. The Kaplan-Meier charts are enclosed as appendix 8.

Table 7-15: Hazard Ratios of admission with comorbidities in patients with PMR vs controls following index date

Comorbidity	**HR (95% CI)**	**Comorbidity**	**HR (95% CI)**
Cancer	0.88 (0.84,0.92)	**Immunological**	7.01 (6.18,7.94)
Breast cancer	0.71 (0.62,0.82)	Rheumatoid arthritis	3.99 (3.31,4.81)
Prostate cancer	0.84 (0.71,0.99)	Osteoarthritis	1.48 (1.42,1.55)
Lung cancer	0.84 (0.74,0.96)	**Endocrine**	1.18 (1.04,1.33)
Colon cancer	0.89 (0.79,1.00)	Hyperthyroidism	0.98 (0.52,1.86)
Melanoma	0.80 (0.61,1.04)	T1DM	1.18 (0.76,1.83)
Leukaemia, lymphoma	0.91 (0.78,1.06)	T2DM	1.41 (1.20,1.66)
Vascular	1.15 (1.11,1.20)	**Neurological**	0.65 (0.58,0.73)
CVD	1.22 (1.13,1.31)	Dementia	0.59 (0.52,0.67)
CCF	1.08 (1.01,1.16)	Parkinson's disease	0.71 (0.53,0.95)
PVD	1.46 (1.32,1.61)	**Psychiatric**	0.91 (0.76,1.10)
CVA	0.93 (0.87,0.98)	Depression	0.97 (0.74,1.27)
HTN	1.12 (0.94,1.35)	Anxiety	0.94 (0.71,1.24)
Respiratory	1.17 (1.09,1.26)	**Fragility fractures**	0.96 (0.91,1.02)
Asthma	1.28 (1.05,1.56)	Osteoporosis	2.09 (1.82,2.40)
COPD	1.13 (1.03,1.23)	Hip fracture	0.90 (0.84,0.96)
Lung fibrosis	1.41 (1.13,1.74)	Wrist fracture	0.97 (0.86,1.11)
Gastroenterological	1.08 (0.97,1.20)	**Ophthalmological**	1.26 (1.21,1.31)
Moderate liver disease	1.11 (0.88,1.41)	Cataracts	1.26 (1.21,1.31)
Peptic ulcers	0.97 (0.84,1.11)	Glaucoma	1.18 (0.98,1.42)
Crohn's disease	1.96 (1.25,3.08)	**Infections**	1.13 (1.09,1.17)
Ulcerative colitis	1.36 (1.01,1.84)	UTI	0.98 (0.79,1.20)
Renal		URTI	1.22 (0.91,1.63)
Renal disease	1.14 (0.94,1.39)	LRTI	1.12 (1.08,1.17)
		Skin infections	1.26 (1.15,1.37)

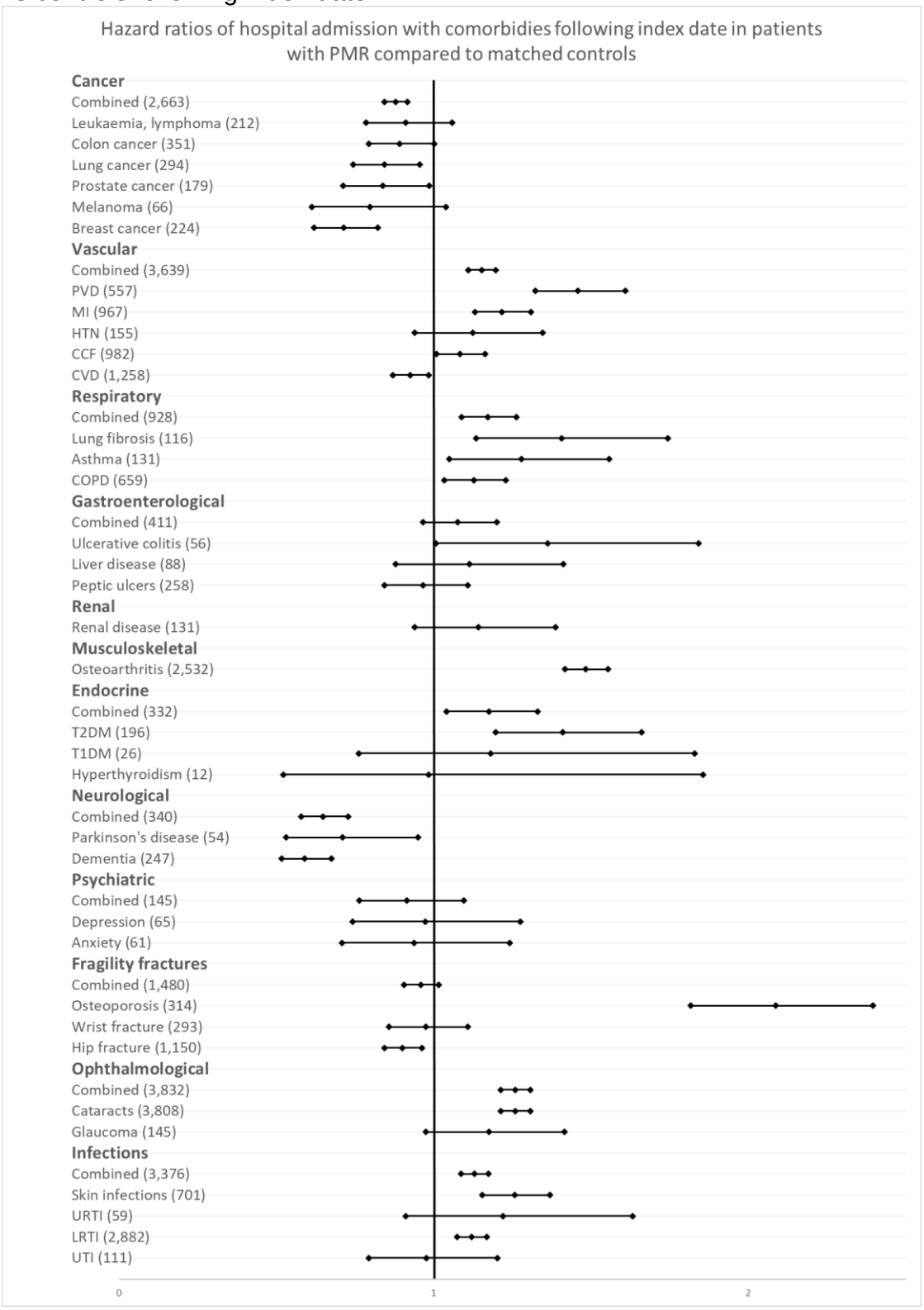
Abbreviations: Cardiovascular disease (CVD), Congestive cardiac failure (CCF), Peripheral vascular disease (PVD), Cerebrovascular disease (CVD), Hypertension (HTN), Chronic obstructive pulmonary disease (COPD), Osteoarthritis (OA), Type 1 Diabetes mellitus (T1DM), Type 2 Diabetes mellitus (T2DM), Multiple sclerosis (MS), Urinary tract infection (UTI), Upper respiratory tract infection (URTI), Lower respiratory tract infection (LRTI)

Hospital admissions with cancer and neurological diseases following index date were significantly less likely in cases compared to controls. However, cases were significantly more likely to be admitted with vascular, respiratory, immunological, endocrine, ophthalmological and infectious diseases. In the case of gastroenterological and renal diseases, as well as fragility fractures, no significant difference was observed.

In the case of the stratified outcomes with a risk of admission greater than 1%, a number of the differences in risk were found to be statistically significant. Outcomes where the risk of admission was higher in controls compared to cases included breast and lung cancer, cerebrovascular disease, dementia and hip fractures. The comorbidities where the increased risk of admission in people with PMR reached statistical significance included cardiovascular and peripheral vascular disease, congestive cardiac failure, asthma, COPD, pulmonary fibrosis, rheumatoid and osteoarthritis, as well as osteoporosis, cataracts, glaucoma and lower respiratory tract and skin infections.

In order to visualise these findings more clearly, they are reproduced in a forest plot, figure 7-8. On this some comorbidities with very strong associations (hazard ratio ≥2) are omitted. These comorbidities include combined immunological outcomes, Crohn's disease and rheumatoid arthritis.

Figure 7-8: Hazard Ratios of admission with comorbidities in patients with PMR vs controls following index date



The next section analyses whether the observed differences in hospital admissions with comorbidity, or the differences in likelihood of comorbid diagnosis observed in chapter 6, impact upon mortality rates in patients with PMR compared to matched controls.

7.3.5 Mortality analysis

The time frame covered by ONS mortality data is different to that covered by HES data, therefore the number of patients contributing data is different in this analysis. Following removal of patients where the index date was prior to the commencement of the study period, a total of 106,744 patients remained for analysis using the ONS mortality statistics. Table 7-16 shows the proportion of excluded patients by case type.

Table 7-16: Number of patients removed from study as index date prior to study start date (ONS)

	Case	**Control**	**Total**
Retained	18,943 (94.3%)	87,801 (94.5%)	106,744 (97.4%)
Not included in the study	1,140 (5.7%)	5,150 (5.5%)	6,290 (5.6%)
Total	20,083	92,951	113,034

Of the patients with linkage established, nearly 95% were included in the mortality analysis and a similar proportion of cases and controls were excluded. However, in order to establish how the reduction in sample size has affected the demographics of the remaining patients, demographic information, including

mean age at index date, sex, region of GP practice, smoking status, BMI category and alcohol consumption are presented in table 7-17.

Table 7-17: Demographic data (ONS sample)

	Total	Case	Control
Age			
Mean (SD)	73.6 (8.9)	73.8 (9.1)	73.5 (8.9)
Sex (%)			
Male	34,559 (32.4)	6,273 (33.1)	28,286 (32.2)
Female	72,185 (67.6)	12,670 (66.9)	59,515 (67.8)
Region (%)			
North East	1,740 (1.6)	306 (1.6)	1,434 (1.6)
North West	13,428 (12.6)	2,366 (12.5)	11,062 (12.6)
Yorkshire & the Humber	3,574 (3.4)	639 (3.4)	2,935 (3.3)
East Midlands	2,853 (2.7)	499 (2.6)	2,354 (2.7)
West Midlands	15,032 (14.1)	2,609 (13.8)	12,423 (14.1)
East of England	15,320 (14.4)	2,674 (14.1)	12,646 (14.4)
South West	17,137 (16.1)	3,042 (16.1)	14,095 (16.1)
South Central	14,075 (13.2)	2,517 (13.3)	11,558 (13.2)
London	7,732 (7.2)	1,456 (7.7)	6,276 (7.1)
South East Coast	15,853 (14.9)	2,835 (15.0)	13,018 (14.8)
BMI category			
Normal(18.5-24.9)	34,552 (32.4)	6,052 (31.9)	28,500 (32.5)
Underweight (<18.5)	1,986 (1.9)	0,221 (1.2)	1,765 (2)
Overweight (25-29.9)	36,515 (34.2)	6,923 (36.5)	29,592 (33.7)
Obese (>=30)	21,521 (20.2)	4,132 (21.8)	17,389 (19.8)
Missing	12,170 (11.4)	1,615 (8.5)	10,555 (12)
Smoking			
Non-smoker	90,111 (84.4)	16,582 (87.5)	73,529 (83.8)
Smoker	11,823 (11.1)	1,827 (9.6)	9,996 (11.4)
Missing	4,810 (4.5)	0,534 (2.8)	4,276 (4.9)
Alcohol			
Never / no current	21,546 (20.2)	3,779 (19.9)	17,767 (20.2)
<10 units per week	55,927 (52.4)	10,369 (54.7)	45,558 (51.9)
10 or more units per week	16,133 (15.1)	2,942 (15.5)	13,191 (15)
Missing	13,138 (12.3)	1,853 (9.8)	11,285 (12.9)
Total time at risk			
Mean (SD)	16.0 (4.4)	16.3 (4.1)	15.9 (4.4)
Pre-index date time at risk			
Mean (SD)	8.1 (4.1)	8.3 (4.2)	8.0 (4.1)
Post-index date time at risk			
Mean (SD)	7.9 (4.6)	8.0 (4.4)	7.9 (4.6)

The average age at diagnosis, sex and region of GP practice were very similar between cases and controls. The mean age of cases was greater than controls, by 0.3 years.

The three disease risk modifiers, BMI, smoking and alcohol consumption, were again broadly similar between cases and controls. Data was less likely to be missing in cases compared to controls, for example 12% of controls had no BMI recorded compared to 8.5% of cases. A higher proportion of cases were recorded as drinking greater than 10 units of alcohol per week (15.5% vs 15%) whereas the control group were again actually more likely to be recorded as smokers in comparison to cases (11.4% vs 9.6%).

The total number and the proportion of patients with PMR and controls who died is shown in table 7-18. Over the total time period, which was on average 8 years of follow up following index date, a higher proportion of cases died compared to controls (31.9% and 31.0%). The mortality rates were similar, at 39.9 and 39.2 per 1,000 patient years for cases and controls respectively. This equated to a non-significant increase in the mortality rate ratio, calculated using Poisson regression, of 1.02 (0.99, 1.05).

Table 7-18: Number and proportion of deaths in patients with PMR compared to matched controls

	Total	**Deaths**	**(%)**	**Rate per 1,000 (95% confidence interval)**
Control	87,801	27,224	31.01	39.2 (38.7, 40)
Case	18,943	6,046	31.92	39.9 (38.9, 41)
Mortality rate ratio			1.02 (0.99, 1.05)	
Total	106,744	33,270	31.17	39.3 (38.9, 39.7)

In order to illustrate the difference in mortality rates between cases and controls, Kaplan-Meier methods were used to construct two survival curves. Figure 7-9 shows survival over the first ten years following index date; while figure 7-10 extends the follow up period to twenty years.

Figure 7-9: Kaplan-Meier plot of survival in first 10 years following index date in patients with PMR compared to matched controls

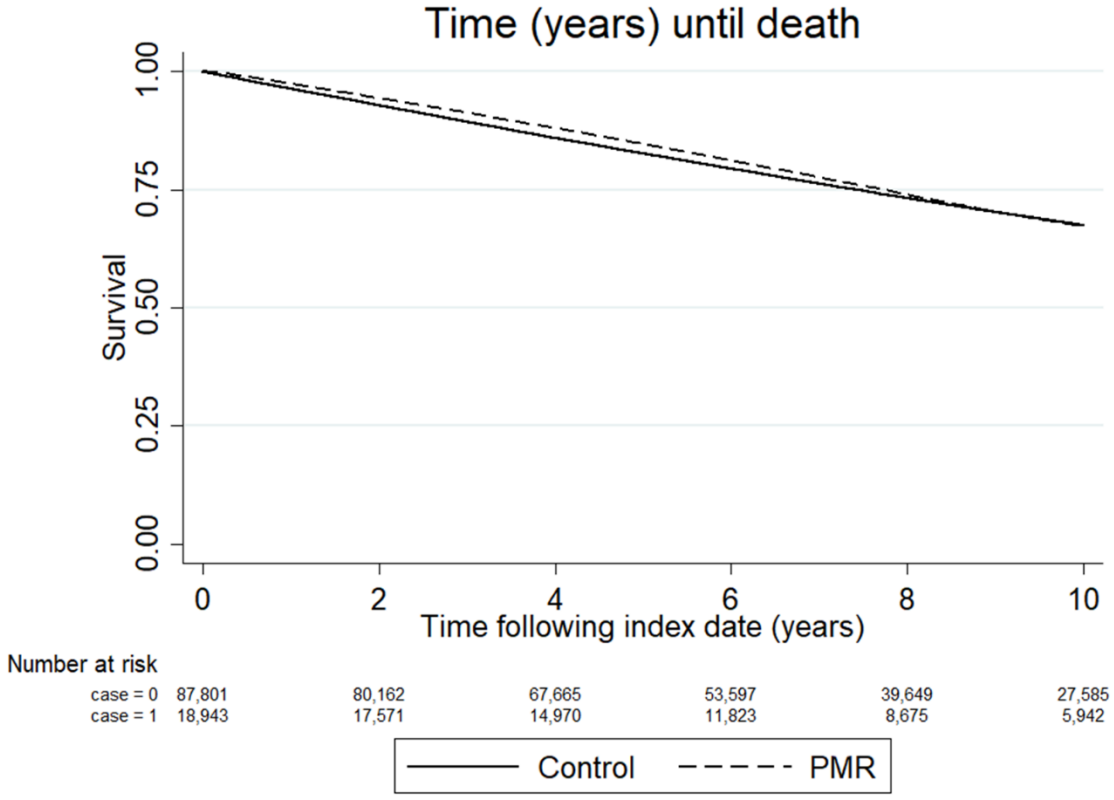
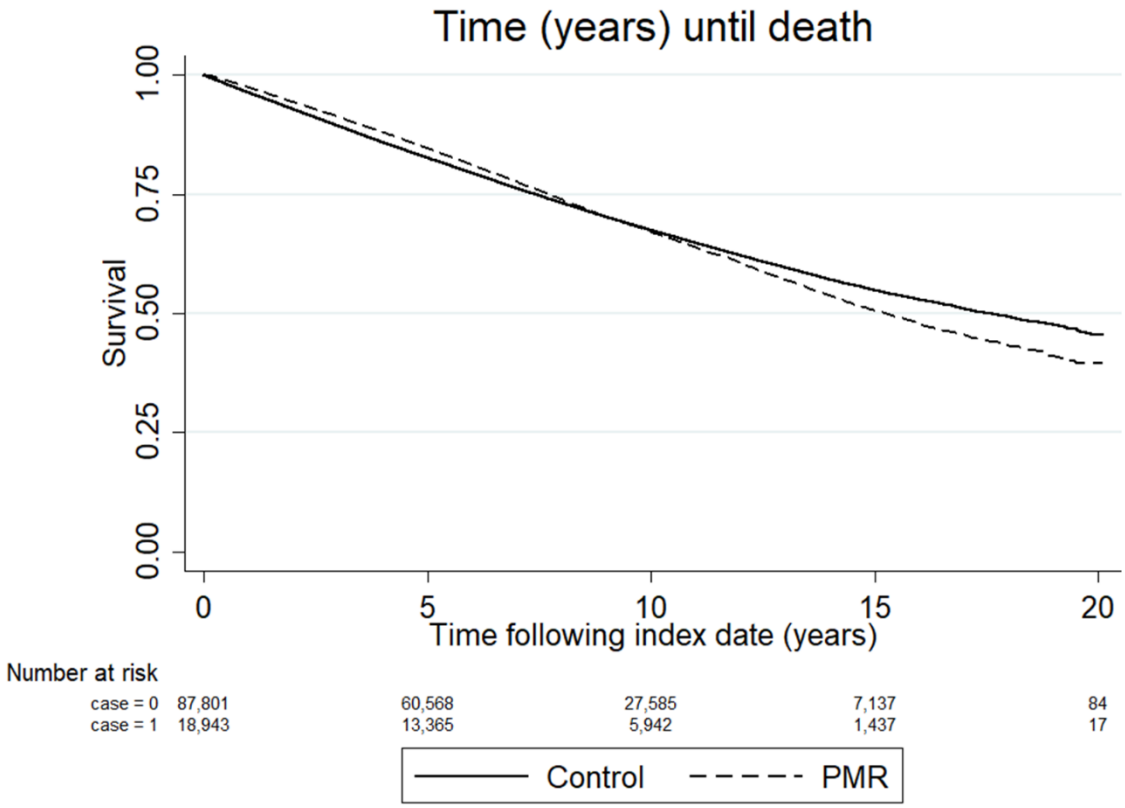


Figure 7-10: Kaplan-Meier plot of survival following index date until end of follow up in patients with PMR compared to matched controls



Although the rate of death is non-significantly increased in patients with PMR, it can be seen that in the first eight years following index date, the proportion of people who died was actually higher in the control group. After around nine to ten years after index date the mortality was higher among patients with PMR. However, the number of patients who were continuing to contribute data to the study at that time reduced considerably.

Causes of death

ONS Mortality data also contains information on the cause of death. The most common causes of death and the proportion of total deaths for cases and controls are shown in table 7-19.

Table 7-19: Causes of death, ICD-10 classification, total number (%)

	Cases		Controls	
1	Chronic ischaemic heart disease	464 (7.7)	Chronic ischaemic heart disease	1,810 (6.7)
2	Acute myocardial infarction	409 (6.8)	COPD	1,652 (6.1)
3	COPD	327 (5.4)	Acute myocardial infarction	1,651 (6.1)
4	Malignant neoplasm: Bronchus or lung	316 (5.2)	Malignant neoplasm: Bronchus or lung	1,631 (6.0)
5	Bronchopneumonia	258 (4.3)	Bronchopneumonia	989 (3.6)
6	Pneumonia	243 (4.0)	Atherosclerotic heart disease	967 (3.6)
7	Atherosclerotic heart disease	187 (3.1)	Pneumonia	889 (3.3)
8	Vascular dementia	123 (2.0)	Alzheimer disease	790 (2.9)
9	Urinary tract infection	115 (1.9)	Malignant neoplasm: Breast	709 (2.6)
10	Malignant neoplasm: Pancreas	109 (1.8)	Vascular dementia	604 (2.2)
11	Cerebrovascular disease	108 (1.8)	Cerebrovascular disease	585 (2.2)
12	Alzheimer disease	106 (1.8)	Malignant neoplasm without specification	460 (1.7)
13	Malignant neoplasm without specification.	103 (1.7)	Malignant neoplasm: Pancreas	447 (1.6)
14	Malignant neoplasm: Breast	99 (1.6)	Urinary tract infection	416 (1.5)
15	Other interstitial pulmonary diseases	93 (1.5)	Malignant neoplasm: Colon	410 (1.5)
16	Congestive heart failure	84 (1.4)	Malignant neoplasm: Oesophagus	371 (1.4)
17	Malignant neoplasm: Colon	84 (1.4)	Malignant neoplasm: Bladder	312 (1.2)
18	Aortic (valve) stenosis	71 (1.2)	Congestive heart failure	309 (1.1)
19	Cerebral infarction	68 (1.1)	Intracerebral haemorrhage	302 (1.1)
20	Malignant neoplasm: oesophagus	67 (1.1)	Other respiratory disorders	291 (1.1)
	Others	2,612 (43.8)	Others	11,629 (41.6)

Of the five most common causes of death there is little variation between cases and controls, all include ischaemic heart disease, acute myocardial infarction, COPD, lung cancer and pneumonia. There are more neoplastic causes of death among controls compared to cases. Among cases, lung, pancreatic, breast and colon cancers, as well as cancers without a specified primary were among the most common causes of death; while in the control group all of these are also seen as well as oesophageal and bladder cancers.

7.4 Discussion

7.4.1 Main findings

This study found that patients with PMR had a similar mortality rate to matched controls. However, they also had an increased risk of non-elective admission to hospital, although on average for a shorter duration. Regarding causes of hospital admissions, there are a number of stratified comorbidities that are either significantly more or less likely to lead to admission in patients with PMR when compared to controls both before and after index date. The conditions where the risk of admission was significantly higher in patients with PMR were asthma and cataracts. The comorbidities with a significantly reduced risk of admission in patients with PMR are breast and lung cancer as well as cerebrovascular disease and hip fractures.

When assessing composite outcomes, patients with PMR were more likely to be admitted to hospital both before and after index date with respiratory, immunological and ophthalmological conditions. Patients without PMR were more likely to be admitted to hospital with any cancer or neurological diagnosis. This study is the first to present a broad, comprehensive view of hospital admissions in a large group of patients with PMR who were diagnosed in primary care. Furthermore, it is the largest study to estimate the effect that a diagnosis of PMR has upon life expectancy and confirms that patients with a diagnosis of PMR do not have a significantly reduced life expectancy.

7.4.2 Strengths and limitations

This study, investigating associations between PMR and mortality and admissions to hospital, utilised a large dataset and a broad range of comorbidities and looked at the period of time before, and after, diagnosis with PMR. The comorbidities were selected using robust methodology and the patient sample used comes from a large, established database of patients who are representative of the UK population. (Williams et al., 2012) As the sample of patients with PMR were drawn from primary care and, as previously discussed, the majority of patients with PMR are managed exclusively in this setting, this sample is therefore highly representative of people diagnosed with PMR in the UK. (Barraclough et al., 2008; Yates et al., 2016)

The linked databases that were used in this study, Hospital Episode Statistics (HES) and Office for National Statistics (ONS) Death Registration data are large, well established and validated sources of information used to guide national healthcare policy. (Herbert et al., 2017) They have been used to report hospital admission rates and trends in mortality for a number of different diseases and health complaints. (Morgan et al., 2017; Parisi et al., 2017; Stewart et al., 2017)

As discussed in chapter 3, a potential limitation is the initial ascertainment of cases. In CPRD it is not possible to authenticate diagnoses by ensuring each patient fulfils validated classification criteria for PMR research. For PMR generally, there are no diagnostic criteria nor specific diagnostic test, therefore even if access to individual patients were possible, confirmation of diagnosis can never be fully achieved. Therefore, ensuring that all patients have at least two GC prescriptions in their records provides more confidence in the diagnosis of

PMR. This method has been used before in previously published studies in CPRD of PMR. (Smeeth, Cook and Hall, 2006)

In this analysis, the comorbidities were coded using the ICD-10 classification system. The use of NHS Digital approved code lists ensures the veracity of the codes that were analysed. Again, however, diagnoses cannot be authenticated by cross checking with symptoms or investigations made. It has long been established that incorrect coding of hospital discharges or death registration data can occur. Some studies have estimated errors in hospital discharge letters of up to 55%, (Tsopra et al., 2019) while others estimate that cardiovascular causes of death may be overstated in mortality data. (Lakkireddy et al., 2004) However, a case study from the ONS found that only 12% of the broad underlying cause of death needed to be amended following medical examiner scrutiny. (Office for National Statistics, 2012b) Furthermore, there is no reason to suppose that the presence of PMR would lead to a difference in error rate compared to those without PMR.

Another potential limitation of this study is a consequence of the deliberate desire to maintain a broad scope within this study. As in the previous investigations in this thesis, there was a risk of multiple testing leading to multiple significant findings. As the confidence interval used to investigate the significance of findings was set at 95%, it is to be expected than 1 in 20 significant findings could have been discovered by chance. However, the aim of this study was to provide an overview of the health of PMR rather than to prove causation, therefore the conclusions of the study are limited to reflect this.

Also, this study looked specifically at hospital admissions. A number of these conditions, particularly autoimmune diseases, present at a younger age, and are unlikely to be coded as the primary reason for an emergency hospital admission in elderly patients. In these cases where very few admissions were recorded, to reduce the risk of overestimating the probability of admission, those outcomes were censored.

Two other potential biases, similar to the previous investigation described in chapter 6, are surveillance bias and diagnostic overshadowing. People who are diagnosed with PMR may be more likely to be followed up more closely in primary care and therefore have more comorbidities recorded in the primary care EHRs However, this is likely to have less effect on the likelihood of admission to secondary care. Finally, better diagnosis of comorbidities may actually lead to improved treatment and therefore case survival. As referenced previously, a Swedish research group found that patients with renal calculi were more likely to have a cancer diagnosis in the years following. (Hemminki et al., 2017) This demonstrates that closer surveillance may lead to earlier detection, and therefore more effective treatment of serious diseases.

The other main potential bias was diagnostic overshadowing, which may have led to the apparent reduction in admissions with neoplastic or neurological diseases. Diagnostic overshadowing, as previously discussed, is the situation in which physical symptoms that a patient may complain of are inadvertently misattributed to a pre-existing illness. (Shefer et al., 2014) This concept could be extended to also include cancer. If patients have a pre-existing diagnosis of cancer they are much less likely to then be diagnosed with PMR as the symptoms

of malaise, pain, stiffness and fever could be attributed instead to their neoplasm. This theory is reinforced by the fact that cancer is regarded as an exclusion criteria in the diagnosis of PMR. (Dejaco, Singh, Perel, et al., 2015)

7.4.3 Summary of hospital admissions with comorbidities and comparisons to existing literature

Vascular disease

The only previous study that assessed the link between PMR and cardiovascular disease using hospital datasets was produced by Pujades-Rodriguez et al. (2016). In this, four linked data sources were used, these included CPRD, the Myocardial Ischaemia National Audit Project disease registry, (Herrett, Smeeth, et al., 2010) HES and the ONS national death registry. In this study, the incidence of fatal and non-fatal CVDs was slightly lower in patients with compared to those without PMR/GCA (adjusted IRR=0.88, (95% CI 0.83 to 0.94)).

When analysing patients with pure PMR, the endpoint “coronary and CVD death composite” was reported. This included stable angina, myocardial infarction, coronary heart diseases not otherwise specified and any cardiovascular death. In this, the incidence rate ratio was reported as 0.91 [0.83, 1.00]. The limitations of this study, as discussed previously, include a limited age restriction such that all adults over 18 years were included, as well as a relatively short mean follow up period of 3.1 years.

In the current study, the mean follow-up period was longer and the number of patients with PMR was larger. The likelihood of a patient subsequently diagnosed

with PMR having a hospital admission with any vascular disease was non-significantly raised prior to index date OR 1.04 [(95% confidence interval) 0.99, 1.10], and significantly increased following index date HR [1.15 [1.11, 1.20]. Furthermore, a higher proportion of cases had chronic ischaemic heart disease listed as a cause of deaths (7.7% vs 6.7%) and the same was true for acute myocardial infarction (6.8% vs 6.1%).

The risk of admission with cardiovascular disease following index date was higher in patients with PMR. As this study looked at hospital admissions, rather than simply a GP Read code, it is unlikely that surveillance bias was the cause for this. This is further evidenced by the fact that death from cardiovascular disease was higher in patients with PMR when compared to matched controls. Therefore it appears, although the difference is small, that there is indeed an increased risk of cardiovascular disease and mortality among patients with PMR.

Cancer

Previous studies into the risk of cancer among patients with PMR have focused on the risk of diagnosis with the disease rather than admission to hospital. The results reported have been equivocal, with some authors suggesting the risk of cancer may be increased following PMR diagnosis, while others did not. (Haga et al., 1993; Myklebust et al., 2002; Jianguang et al., 2010; Muller et al., 2014; Pfefiffer et al., 2015; Bellan et al., 2017) In chapter 6, the risk of cancer diagnosis in a patient's primary care record was seen to be significantly lower among patients with a diagnosis of PMR.

The risk of admission to hospital with a cancer diagnosis as the primary problem was reduced in patients with PMR when compared to matched controls. This reduction in risk was present both before and after index date. The reduction in the risk of cancer diagnosis was also reflected in mortality data. Overall, of the top 20 causes of death, 11.7% of PMR cases were cancer related, compared to 16% of controls.

Again, diagnostic overshadowing may still play a part in this result. As PMR classification criteria make clear, cancer is considered a differential to be excluded rather than a potential comorbidity with PMR. (Dasgupta et al., 2012; Dejaco, Singh, Perel, et al., 2015) Therefore it may be that this apparent 'protection' that PMR provides against neoplastic disease diagnosis or mortality is rather a result of a reluctance to make a diagnosis of PMR in patients with cancer.

Furthermore, the mainstay of treatment for PMR, glucocorticoids, are often used in the management of cancer. This is because the GCs are potent anti-inflammatories and often have side effects beneficial for patients with cancer, such as increased appetite and energy levels. GCs are also considered safe to use in cancer as the GC receptor is not considered an oncogene. (Pufall, 2015) Therefore, it may be that patients with cancer may develop PMR, but due to the fact the treatment for cancer can also include GC therapy, their symptoms would improve or resolve with the GCs and therefore not be identified as a PMR case.

Autoimmune

As discussed previously, whether PMR is an autoimmune or auto-inflammatory disease remains a matter of debate. (Floris et al., 2018) Pertaining to this, an epidemiological study of the co-existence of 33 autoimmune conditions, including PMR, was conducted in Denmark by Eaton et al (2010). They found, among patients with PMR, an increase in the risk of Sjogren's disease, systemic lupus erythematosus, systemic sclerosis, psoriatic arthritis, ulcerative colitis and Crohn's disease. This study also found an increase in the risk of multiple sclerosis (MS) in patients with PMR.

In this study of hospital admissions, the rarity of a hospital admission being recorded as primarily due to an autoimmune condition meant that any associations were difficult to define. This is in part due to the relatively advanced age of the cases and controls, averaging over 70 years, as many of the autoimmune conditions present in younger age groups. Of the autoimmune conditions, there were enough admissions for rheumatoid arthritis (RA) only, both before and after index date, to calculate likelihood ratios. Prior to index date, the risk of admission was significantly lower in people who went on to develop PMR compared to controls. After diagnosis this pattern was reversed. Again, similar to the outcomes with cancer, it may be that in patients with an existing diagnosis of RA clinicians are less likely to subsequently diagnose PMR.

When the outcomes were combined, the risk of admission with any autoimmune condition was higher both before and after index date. Therefore it appears, in corroboration of the CPRD data, PMR is strongly linked to autoimmune

conditions, but to demonstrate a link to admissions with specific comorbidities is difficult in linked data due to the rarity of admissions.

Glucocorticoid related conditions

As previously discussed, a recent cohort study of 359 patients from the United States assessed the likelihood of GC related complications in patients with PMR. (Shbeeb et al., 2018b) This study found no significant differences in almost all measured outcomes, including diabetes mellitus, hypertension, hyperlipidaemia and hip, vertebral or Colles' fracture. The only outcome in which a statistically significant outcome was noted was the incidence of cataracts Hazard ratio (HR) 1.72 [1.23, 2.41]. A study from the UK based on CPRD by Paskins et al. (2018) found that in patients with PMR and GCA the rate of fragility fractures were increased.

Many of the findings from the analysis of comorbidities in CPRD were borne out in this study of hospital admissions. Again, patients with PMR were significantly more likely to have an admission due to ophthalmological conditions and infectious diseases. However, the risk of admission due to a fragility fracture was not demonstrated to be significantly different, although in chapter 6, it was noted that patients with PMR had an increased risk of diagnosis with osteoporosis. This may reflect that GPs are aware of the risk of prolonged GC treatment with regards to bone mineral density. Therefore patients with PMR may be referred for the correct investigation and treatment to prevent complications such as hip fractures developing.

Another potential reason could be that, as discussed in chapter 6, patients with a previous diagnosis of cancer are less likely to be diagnosed with PMR. Cancer is a known risk factor for pathological fractures. Therefore, it may be that the excess risk of pathological fracture in the control group is similar to the excess risk of fracture conferred by the use of long term GC therapy in the PMR group.

Regarding infectious diseases, it is likely that the immunosuppressive actions of GCs do indeed mean that patients on long term GC therapy are at higher risk of developing infectious diseases. Furthermore, the risk of admission with the well-recognised ophthalmological complications of GC therapy- that of cataracts and glaucoma- was seen to be higher in patients with PMR.

Other comorbidities

Psychiatric

Previous studies have found no association between PMR and psychiatric comorbidities such as schizophrenia (Eaton et al., 2006; Chen et al., 2012) and bipolar disease, (Eaton et al., 2006). In this study, due the very small numbers of patients who were admitted to hospital with these conditions, it was not possible to draw a conclusion as to whether having a diagnosis of PMR affects this measure.

The risk of admission due to depression and anxiety was not found to be significantly different in cases and controls. Again, this reflects the rarity of admissions due to these causes in this age group rare.

Neurological

One previous study found an increase in the risk of Parkinson's disease in patients with PMR. (Kari Hemminki, Li, et al., 2012) In chapter 6 it was found that the risk of serious neurological conditions, such as Parkinson's disease, MS and dementia was significantly lower in patients with PMR prior to index date. The possibility that this risk reduction was due to diagnostic overshadowing was discussed. When looking in this analysis at the rates of hospital admission, with a neurological diagnosis being the primary reason for stay in hospital, the small numbers of patients admitted precluded the calculation of a likelihood ratio for most outcomes. However, it was seen that the risk of being admitted following index date with dementia or Parkinson's disease was lower in patients with PMR compared to controls.

Again, the reason for this may be that the rates of PMR in patients with these conditions may be similar but due to diagnostic overshadowing PMR is under-diagnosed in these groups. Although not specifically relating to PMR, it is becoming better recognised that chronic pain in elderly patients with cognitive decline is under-diagnosed. (Cravello et al., 2019)

Endocrine

The risk of admission due to type one diabetes was not significantly different before or after index date. However, although the risk of admission due to type 2 diabetes was no different in patients with PMR before index date, it became significantly higher after index date. This may be due to GC treatment either

increasing the risk of type two diabetes developing or existing type two diabetes becoming uncontrolled and necessitating admission.

Renal and Respiratory

As discussed in chapter 5.4, existing literature does not contain estimates of the risk of respiratory and renal diseases in patients with PMR. As such, this is the first study to estimate these figures. Prior to diagnosis, the risk of admission due to renal disease is significantly lower in those who went on to develop PMR. After index date there was no significant difference. In chapter 6 it was seen that renal disease was more likely to be diagnosed in patients with PMR, but it does not appear to mean consequently, that patients are more likely to receive hospital treatment for the same.

Prior to index date the risk of admission due to asthma was significantly higher in patients with PMR, however the risk of admission due to COPD or lung fibrosis were not significantly different. Following index date, the risk of admission was significantly higher in all three respiratory conditions. The increased risk of diagnosis and admission with respiratory conditions has not previously been noted. It may be that there is a shared pathological process between PMR and these respiratory diseases, particularly as all three conditions have an inflammatory, GC responsive, pathophysiological process.

7.4.4 Hospital admissions

One previous investigation into hospital admission rates in patients with PMR has been published. It was presented as an abstract at the American College of Rheumatology annual meeting and found that patients with and without PMR had similar rates of hospitalisation (rate ratio 1.03 [0.95, 1.11)) and that the average length of stay was 4.4 and 4.7 days in patients with and without PMR respectively. (Raheel et al., 2018)

In this study, however, the admission rate was found to be significantly higher in patients with PMR. The median duration of admissions for cases and controls was the same at 5 days, although a higher proportion of controls had slightly longer admissions. Both of these findings are similar to that reported in the previous analysis by Raheel et al (2018). In this analysis, the mean length of stay (with 95% confidence intervals) was 10.6 (10.4, 10.8) for patients with PMR, while in controls it was 11.4 (11.4, 11.6). This shows the length of stay was significantly greater in controls. However, the fact the mean duration of stay was much greater than the median was likely caused by a small number of very prolonged admissions. As a result of this, the median value provides a clearer insight into the average length of stay. This phenomenon has been noted before in analyses of length of hospital admissions. (Lee, Fung and Fu, 2003)

The increased rate of hospital admission is apparent from the index date and persisted throughout the follow up period. Furthermore, patients with PMR were found to be more likely to have multiple admissions within each measured time period up to 2 years after index date.

7.4.5 Mortality analysis

Four previous studies have estimated mortality in patients with PMR, with three of the four studies demonstrating reduced levels of mortality (Gran et al., 2001; Doran et al., 2002; Myklebust et al., 2003), and one an increase in mortality. (Uddhammar et al., 2002) However, the number of patients with PMR included in these studies were much smaller than in this analysis, at 398, 378, 315 and 35 for Gran (2001), Doran (2002), Myklebust (2003) and Uddhamer (2002) respectively.

In this study, over the first 8 years following index date, the mortality rate was slightly lower in patients with PMR compared to controls. However, over the entire study period, there was found to be no significant difference, with an incident rate ratio of 1.02 [0.99, 1.05]. This study therefore provides further evidence that PMR does not affect mortality and is therefore reassuring for those who receive a diagnosis of PMR.

The causes of death are similar between cases and controls. However, there is a small increase in the number of patients who died from vascular diseases among cases and a corresponding decrease in those recorded to have occurred due to neoplasms.

7.4.6 Conclusion and clinical implications

This study is the first to estimate the rate and reason for hospital admissions before and after diagnosis in patients with PMR and matched controls.

Furthermore, it is the largest sample of PMR to provide an estimate of the effect that PMR has on mortality. In conclusion, patients with PMR are more likely to be admitted to hospital compared to matched controls, although when they are admitted it is for a slightly shorter duration.

Both before and after index date, patients with PMR are significantly more likely to be admitted to hospital due to asthma and cataracts and significantly less likely to be admitted due to breast or lung cancer as well as cerebrovascular disease and hip fractures. Overall however, the mortality rate in patients with PMR, when compared to matched controls, is not significantly different, although there are some minor variations in the recorded cause of death.

The most important observation is that, although patients with PMR are more likely to be admitted to hospital, the overall mortality rate is no different.

The reason for increased hospital admissions in patients with PMR may be related to their index condition, as some may have been initially diagnosed in hospital. Following this period immediately after index date, the increase in the rate of admissions may be due to surveillance bias, with more intensive follow up and testing such that patients with PMR are more likely to then be admitted to hospital for further management.

The comorbidities that are associated with an increased risk of admission to hospital before and after index date in patients with PMR include asthma and glaucoma. After index date, a 15% increase in the risk of admission due to vascular disease was noted. In patients without PMR, they were significantly more likely to be admitted to hospital with neurological and neoplastic conditions.

However, despite the increased risk of admission due to vascular causes and reduced risk of admission with neoplastic disease, the overall mortality rate among cases and controls was similar.

The risk of admission due to most glucocorticoid related side effects following index date was greater in patients with PMR compared to controls. These comorbidities included ophthalmological and infectious diseases. This is likely due to GC therapy either causing impairment of the immune system in patients with PMR or as a result of a known complication of GC treatment. Both of these types of complications, unfortunately, cannot be prevented by any prophylactic treatment aside from simply reducing and stopping GC therapy. However, as discussed in chapter 4, a large proportion of patients are subject to prolonged GC therapy. In contrast to this, the risk of admission due to fragility fractures was not found to be significantly different, this could reflect that, although a diagnosis of osteoporosis is more likely in patients with PMR who are prescribed GC treatment, the risk of a fragility fracture can be mitigated by effective preventative treatment by GPs. In order to prevent these complications, future research may need to investigate different approaches to the treatment of PMR. This could mean either an emphasis on rapid reduction of GC therapy, or earlier transfer to steroid sparing medications in susceptible patients.

Finally, the risk of admission with asthma was significantly higher before and after index date. This is not a comorbidity that has been comprehensively investigated in the past. Given that, as discussed earlier, PMR shares many features with asthma, future research priorities could be to explore whether there are any shared autoimmune pathways involved in the development of these conditions.

The final chapter in this thesis is the conclusion, to draw together the findings of each of the previous chapters.

Chapter 8 CONCLUSION

8.1 Main findings

This thesis examined the epidemiology of polymyalgia rheumatica (PMR) in the UK. Using a large, validated and nationally representative database, five different studies were conducted to describe, understand and compare various aspects of PMR epidemiology, including the incidence and prevalence of PMR, PMR treatment, the comorbidity burden associated with PMR, hospital admissions and mortality. The main findings are as follows:

1. PMR affects 1 in 120 adults aged over 40 in the UK.
2. PMR is more common in women than men.
3. The prevalence of PMR increases with age, and has the highest incidence in over 70s.
4. Since the new century, the incidence of PMR has been steady in patients aged over 40, ranging from 90-100 new cases per 100,000 person years.
5. The median time to stop continuous GC treatment was 1.31 years (IQR 0.65, 2.6).
6. The median time to discontinue all GC treatment was 1.93 years (0.95, 4.03).
7. There is a strong association between duration of treatment and total GC dose.
8. The existing evidence investigating the association between PMR and key comorbidities is currently lacking and hindered by low quality studies

9. There is a statistically significant increased risk of vascular, respiratory, renal, autoimmune, endocrine and psychiatric diagnoses in patients with PMR both before and after diagnosis.
10. There is a statistically significant reduced risk of diagnosis with cancer and dementia in patients with PMR both before and after diagnosis.
11. Patients with PMR are more likely to be admitted to hospital following diagnosis compared to age and sex matched controls.
12. People with PMR do not have an excess mortality risk and PMR does not affect life expectancy

This chapter will summarise the main findings of this thesis, a detailed epidemiological study of PMR. Findings discussed will include the incidence, prevalence and treatment of PMR, as well as comorbidities, hospital admissions and the mortality rate associated with PMR. Further to this, the main strengths and weaknesses, as well as clinical implications and conclusions of the thesis will be presented.

8.2 Incidence and prevalence

The prevalence of PMR among patients aged over 40 years old in the UK is 0.85%. This equates to one patient who has received a diagnosis with PMR for every 120 of the population of this age, or approximately 280,000 people. Although the incidence of PMR was steady after the year 2000, point prevalence of PMR increased over the study period of 1990-2015, due to the aging population.

The case definition for PMR used in this study was a diagnostic code and evidence of two prescriptions of glucocorticoid (GC) therapy in the primary care electronic health record (EHR). Of the two GC prescriptions, the first must be within six months of diagnosis date and the second within six months of the previous prescription. This case definition has been used previously in CPRD studies of PMR incidence and prevalence.

PMR was found to be 67% more common in women, reflecting the findings of previous PMR research and the pattern observed with most autoimmune diseases. The prevalence of PMR increases with age. PMR is very rare under the age of 60 years, but then increases with each successive decade thereafter. This correlates with existing estimates of the median age of diagnosis between 70 to 75 years of age.

The epidemiology of PMR shows substantial variation both between, and within, countries. Worldwide, PMR has higher prevalence at more northerly latitudes. However, within the UK, the regional variation is inverted. The southern regions of the UK show a higher incidence and prevalence when compared to northern areas. This pattern has been observed previously. The increased risk of diagnosis with PMR in southern regions of the UK is unexpected, as patients in these areas tend to have better health and longer life expectancy. As PMR diagnosis rates increase with age, the increased incidence in the south of the UK could be due to an older population, but the increased rate remained following adjustment for age. In chapter 6 it was seen that patients with a pre-existing diagnosis of cancer or neurological conditions were less likely to then be diagnosed with PMR. Therefore, it may be that PMR is preferentially diagnosed in patients without severe, enduring comorbid disease. Another reason for the

difference in incidence could be variations in genetic susceptibility to PMR between different UK regions, however this is probably unlikely due to the relative homogeneity of the genetic composition of the UK. Therefore, other reasons such as a link to vitamin D exposure, socio-economic status, or as part of the generalised increase in autoimmune diseases in higher income countries (*British Society of Immunology*, 2016) could be postulated as playing a role in the increased prevalence in the south of the UK.

The incidence of PMR in patients aged over 40 in the UK during the period 1990-2016 was 95.9 per 100,000 patient years. The most recent previous estimate found that the incidence of PMR was 84 per 100,000 person years. Furthermore, this study found that the incidence of PMR was increasing over the time period 1990 – 2001. The current study replicated this increase in incidence until the year 2000. However, after that time the incidence rate plateaued. The prevalence of PMR continued to rise over the whole study period however. This could be for a number of reasons. First, as the population ages, a greater proportion of people are of an age where they are susceptible to PMR. Second, PMR is a chronic disease, which is not known to have a significant impact on mortality; therefore, once a patient has been diagnosed they remain part of the prevalent pool. Finally, CPRD coverage began close to the start of the study period, therefore diagnoses with PMR that occurred prior to this date may not have been recorded, leading to a slight underestimate of prevalence in the first years of the study.

8.3 Treatment of PMR

PMR is treated almost exclusively using glucocorticoids (GC). This thesis examined current treatment patterns of GCs for patients with a diagnosis of PMR in the UK. This was then compared to existing guidelines. The length of GC treatment was associated with the total dose of GC received. The end of treatment was defined in three ways, either as a gap of 90 days, or six months, between consecutive prescriptions, or until no further GCs were prescribed. In these cases, the median time to end of treatment was 1.31, 1.88 and 1.91 years, respectively. Treatment guidelines for PMR suggest that treatment should conclude two years after diagnosis and, as such, these findings suggest that 'best practice' is being followed. However, a proportion of patients are subject to prolonged GC treatment. In this study, when total therapy was considered, 25% of patients received more than 4 years of GC treatment. This confirms the presence of a 'symptom tail' of GC therapy in patients with PMR.

The average daily dose of GC treatment was 5mg and the initial dose received was between 8-21mg in 50% of patients. The average dose and initial dose received therefore correlated well with clinical guidance. Most patients with PMR in the UK complete GC therapy in a timely manner at appropriate doses. However, the identification of patients who may be subject to prolonged GC therapy should be a priority for future research in order that they can be referred to secondary care at an early stage for consideration of 'steroid sparing' therapy. (Dejaco, Singh, Perel, et al., 2015)

8.4 PMR and comorbidities

Comorbidities are commonly found in people diagnosed with PMR, as would be expected from the demographics of the study population. The overall comorbidity burden of patients with PMR was compared to controls matched by age, sex and practice using the Charlson comorbidity index. Patient with PMR had more comorbidities at one, two and five years prior to diagnosis. Furthermore, there was a statistically significant increase in the risk of diagnosis with vascular, respiratory, gastroenterological, immunological, endocrine, psychiatric ophthalmological and infectious diseases in patients with PMR. However, there was also a statistically significant reduction in the risk of diagnosis with cancer or a neurological disease.

A similar pattern was seen after diagnosis of PMR. The overall burden of disease, measured by the Charlson comorbidity index, was higher in patients with PMR compared to controls, at diagnosis as well as one, two, five and ten years later. Further to this, and following exclusion of prevalent cases, a significant increase in the risk of new diagnoses with vascular, respiratory, gastroenterological, autoimmune, endocrine, psychiatric, and ophthalmological diseases was observed in patients with PMR after index date. Again, however, the risk of diagnosis with cancer or neurological diseases was significantly reduced in patients with PMR.

Current clinical classification criteria suggest that when making a diagnosis of PMR, clinicians should actively exclude other ‘mimicking’ conditions such as rheumatoid arthritis, endocrine, infective and neoplastic conditions. (Dejaco, Singh, Perel, et al., 2015) These guidelines, as well as diagnostic

overshadowing, may account for part of the reason that the risk of cancer was lower in patients with PMR.

It may be more clinically pragmatic in future, therefore, to amend guidelines, specifically allowing for the diagnosis of PMR in the presence of comorbidities such as cancer. Another approach may be, through disseminating the findings of this thesis in scientific literature, increasing clinician awareness of the fact that PMR may be underdiagnosed in patients with serious underlying medical conditions such as cancer or neurological diseases. Furthermore, greater emphasis should be placed in the education of clinical practitioners that the clinical classification criteria were not designed or intended for use as diagnostic criteria, and only exist to guide recruitment into clinical trials.

Previous studies investigating comorbidity in people with PMR have primarily focused on the likelihood of patients with PMR developing vascular disease and cancer, with some smaller studies looking for associations with other autoimmune conditions. This study has found that there does appear to be an increase in the risk of diagnosis with vascular disease in the years following diagnosis with PMR. The data in this thesis suggests that PMR is strongly associated with other autoimmune diseases. However, due to the rarity of some of these conditions, and the relatively advanced age at which PMR is diagnosed, there were often quite small numbers of patients captured by these analyses. However, the observed association with other autoimmune conditions reinforces the idea that PMR should also be regarded as an autoimmune or auto-inflammatory condition.

Further to this, although previously no other investigation has looked into associations with respiratory conditions, the risk of diagnosis with asthma was significantly increased both before and after diagnosis in patients with PMR.

A number of findings which were unexpected were also seen in this study. For example, although the risk of osteoporosis was significantly greater in patients with PMR, the risk of hip fractures were significantly reduced prior to index date, and not significantly different after, in patients with PMR. Given the prolonged duration of glucocorticoid therapy, it is surprising that the risk of hip fracture was not much greater in patients with PMR. It may be that clinical practitioners are more aware of the increased risk of osteoporosis in patients with PMR and so are referring patients appropriately for investigation and subsequent treatment. This could explain the increased risk of osteoporosis and the neutral effect on risk of hip fracture. A further complicating factor is that patients with PMR are less likely to have a previous diagnosis of cancer. As metastatic cancer is a recognised cause of pathological fractures, it may be that under diagnosis of PMR in this group leads to an underestimate of the burden of hip fractures in patients with PMR.

Another unexpected finding was the significantly increased risk of asthma and COPD in patients with PMR, despite the fact that they were less likely to be recorded as smokers. This could be due to a number of factors. Patients with asthma may indeed be less likely to smoke, as it would exacerbate their condition. However, as COPD is strongly linked with tobacco exposure, and more common in patients with PMR, it is surprising that the rate of smoking is reduced in this group. In this thesis, as per other CPRD studies, smoking status was defined by three categories- current smokers and those where data were

missing, as well as never- and ex-smokers, who were included in the same category. The most recent record of smoking status to index date was used. It may be that patients who developed COPD are more likely to have stopped smoking to prevent further lung damage, and therefore a higher proportion of patients with PMR were ex-smokers rather than never-smokers when compared to controls.

Finally, as the treatment for PMR is a course of glucocorticoids, which in many cases is of prolonged duration, it is important to assess the risk of GC related complications. An increased risk of vascular disease, hypertension, type two diabetes, peptic ulcers, osteoporosis, cataracts and glaucoma was indeed demonstrated among patients with PMR. This finding itself may in part be due to surveillance bias, in that patients receiving GC therapy are followed up more intensively to monitor for complications, which could cause an apparent increase in the risk of diagnosis with these conditions.

8.5 Hospital admissions and mortality

The increased rate of comorbidities seen in patients with PMR translated into an increased hospitalisation rate following diagnosis. Patients with PMR were 18% more likely to be admitted to hospital following diagnosis compared to their matched controls, although the average duration of admission among patients with PMR was shorter. Regarding reasons for admission, a statistically significant increase in admissions due to asthma or cataracts was observed in patients with PMR. Equally, however, a statistically significant decrease in the risk of

admission in patients with PMR was also observed with either breast or lung cancer, as well as cerebrovascular disease and hip fractures.

The increase in the risk of admission due to cataracts is to be expected given the necessity for prolonged GC therapy. However, the increased risk of admission with asthma suggests again that there may be a shared pathogenesis between PMR and asthma.

The overall increased rate of hospital admissions did not lead to an increase in the mortality rate among patients with PMR, however. This reflects what has been seen in previous, albeit smaller, studies into mortality in PMR. The causes of death in patients with PMR were broadly similar compared to their matched controls, although a slightly higher proportion of patients with PMR died due to vascular causes and a slightly lower proportion died due to neoplastic conditions.

In this study it was demonstrated that patients with PMR were less likely than controls to have a previous diagnosis of cancer. Therefore, it could be speculated that if PMR has a neutral effect on survival then, through the exclusion of patients with cancer, the PMR group should actually have improved survival when compared to matched controls. It may be that this is mitigated by the increased rates of vascular disease in patients with PMR that were seen after index date. The overall consequence of these two effects may be that net survival is similar.

8.6 Strengths and weaknesses

This thesis used the CPRD database to create a detailed picture of the epidemiology of PMR. There are several strengths to the work in this thesis. First,

CPRD is a large database that is representative of the population of the UK. Therefore, selection bias was minimised. Second, this database consists of data collected in the course of routine clinical care. It is therefore a reflection of genuine day-to-day clinical practice. This contrasts with the data that may be recorded during a prospectively recruited cohort study. Third, this is the first study that has described treatment patterns in patients with PMR as well as the comorbidities that were present before and after diagnosis, as well as the likelihood of, and reasons for, admission to hospital. Fourth, the methods used in this study have been used in previous CPRD epidemiological studies. Finally, although making estimates of the incidence, prevalence and mortality of patients with PMR has been performed previously, this study is novel in the size of the sample and duration of follow up, both of which are much greater than previously seen.

A criticism of the database could be that it was not possible to corroborate each diagnosis with a patient's clinical notes. Regarding PMR diagnosis, the use of two GC prescriptions to justify case selection is well established, and the vast majority of patients fulfilled this criterion, suggesting that the diagnostic code was correctly applied to most patients. To improve the study, criteria to validate the diagnosis formally could be created for CPRD; however, this would be complicated by the lack of formal diagnostic criteria for PMR.

The same criticism could be made regarding the diagnosis of comorbidities. Again, it was not possible to corroborate each comorbid diagnosis with the clinical record for each patient. However, reassuringly, often the findings from the case control and cohort studies, such as an increased risk of vascular disease and reduced risk of cancer diagnoses were subsequently replicated in the analysis of

linked data, including hospital admissions and mortality data. The fact these findings were consistent across multiple datasets using primary and secondary care data and, crucially, different coding systems (Read codes and ICD-10), provide reassurance that the diagnoses are accurate.

Finally, a further weakness of the CPRD is that of missing data. Information in electronic health records in primary care is collected in the course of routine clinical care, rather than specifically for research, therefore records are not always fully complete. For example information about risk factors, such as smoking, blood pressure, alcohol intake and BMI, which may influence whether patients develop a wide range of comorbidities, may be missing. However, as electronic health records have been in existence for around two decades, and also due to the impact of the quality outcomes framework incentivising general practices to record administrative data (Roland, Guthrie and Thome, 2012), the proportion of patients where data is missing has reduced markedly in the last twenty years. (Herrett, Bhaskaran, et al., 2015)

8.7 Relevance to clinical practice and research

Clinically, this thesis has proven that a large proportion of patients with PMR receive large doses of GCs therapy. Furthermore, there is an increase in the risk of GC related side effects overall in patients with PMR. Therefore, the identification of patients who may be subject to prolonged GC therapy should be a priority at the earliest stage possible in their diagnosis and subsequent treatment journey. This is in order that they could be considered for ‘steroid

sparing' therapy, as per current PMR guidelines. (Dejaco, Singh, Perel, et al., 2015)

The strong association seen between PMR and other autoimmune and auto-inflammatory conditions suggests that future research could examine whether specific auto-antibodies for PMR can be identified. This would also assist in the diagnostic process. Further to this, the identification of genetic markers that cause an individual's risk of PMR to be elevated could be another research priority.

Moreover, patients with PMR were found to have a statistically significant increase in the risk of diagnosis, both before and after index date, with asthma. As both PMR and asthma have a, currently, undefined polygenic basis of susceptibility; it may be a productive area for future research to assess whether there is either a shared genetic pathway. Another area of research could be to assess whether the early exposure to repeated doses of glucocorticoid therapy that is seen in asthma could be a part of the reason for the significantly increased risk of asthma prior to index date in patients with PMR.

The question of whether previous exposure to glucocorticoids may have an effect on the likelihood of later development of PMR could be addressed using the CPRD database. However, as discussed previously, as data collection for CPRD began in 1990, this may not be early enough to provide this answers. Other ways to investigate this hypothesis may involve case control studies of patients recruited following a new diagnosis of PMR in primary care, however this may be subject to recall bias.

Finally, it appears that a diagnosis of PMR appears to have a neutral effect on mortality. However, the case control study found that patients with PMR were less likely to have received a previous diagnosis of cancer. Once the findings from this thesis are publicised in peer review journals, a more inclusive approach to the diagnosis of PMR may be encouraged. This may then address the possible under diagnosis of PMR in patients with cancer. After this, it may be necessary to re-evaluate the effect PMR has on mortality. The neutral effect of PMR on mortality observed in the current study may be caused by the increase in the risk of vascular disease in this patient group balancing the reduction in the risk of previous cancer diagnosis among patients with PMR. Therefore, following inclusion of these patients, the risk of mortality may actually rise slightly in patients with PMR.

8.8 Final conclusion

In conclusion, the CPRD has been used successful to answer a number of important epidemiological and clinical research questions. This thesis provides comprehensive evidence of the epidemiology of PMR in the UK, including incidence, prevalence, treatment patterns, comorbidities, hospital admissions and mortality. The methodologies used in this study can further be applied to other, similarly under-researched conditions.

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APPENDICES

APPENDIX 1: ISAC application form

PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No. Submission date	..17_023..... ...17/10/2017... ..	***IMPORTANT*** *Please refer to the **guidance** for '**Completing the ISAC application form'** found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.*

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title§ (*Please state the study title below)*

Polymyalgia rheumatica in primary care: an epidemiological investigation into occurrence and comorbidities.

§*Please note: This information will be published on the CPRD's website as part of its transparency policy.*

2. Has any part of this research proposal or a related proposal been previously submitted to ISAC?

Yes * ☐ No ☒

3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)

Yes* ☐ No ☒

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☐	Methodological Research	☐
Health/Public Health Services Research	☐	Other*	☐

5. Health Outcomes to be Measured§

§*Please note: This information will be published on CPRD's website as part of its transparency policy.*

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- Incidence and prevalence of polymyalgia rheumatica (PMR)
- Comorbidities in patients before and after PMR diagnosis

6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals ☒ Presentation at scientific conference ☒
Presentation at company/institutional meetings ☒ Regulatory purposes ☐
Other* ☐

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator§

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.
Dr Alyshah Abdul Sultan, Research Fellow, Keele University, a.abdul.sultan@keele.ac.uk

§*Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy*

CV has been previously submitted to ISAC ☒ **CV number:** **14_191**
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

8. Affiliation of Chief Investigator (full address)

Institute for Primary Care and Health Sciences
Keele University
Staffordshire
ST5 5BG

9. Corresponding Applicant§

Please state the full name, affiliation(s) and e-mail address below:
Dr Richard Partington, Clinical Research Fellow, Keele University, r.partington@keele.ac.uk
§*Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy*
Same as chief investigator ☐
CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

10. List of all investigators/collaborators§

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

§*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: Dr Sara Muller, Keele University, s.muller@keele.ac.uk
CV has been previously submitted to ISAC ☒ **CV number:** 15_165
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Professor Christian Mallen, Keele University, c.d.mallen@keele.ac.uk
CV has been previously submitted to ISAC ☒ **CV number:** 073_15CESP
A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator: Dr Toby Helliwell, Keele University, t.helliwell@keele.ac.uk
CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☒

11. Conflict of interest statement*
Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work
The authors declare no conflict of interest, financial or otherwise, with respect to this work; we had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

12. Experience/expertise available
Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	**Yes**	**No**
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Dr Alyshah Adbul Sultan and Dr Sara Muller are qualified and experienced in a range of statistical techniques	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Dr Alyshah Abdul Sultan and Dr Sara Muller have previously worked on a number of large CPRD studies	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Dr Richard Partington, Professor Christian Mallen & Dr Toby Helliwell are all practising GPs in the West Midlands and Northwest of England	☒	☐

13. References relating to your study
Please list up to 3 references (most relevant) relating to your proposed study:

1. Smeeth L, Cook C, Hall a J. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. *Ann Rheum Dis*. 2006;65(8):1093-1098. doi:10.1136/ard.2005.046912.
2. Kuo C-F, See L-C, Luo S-F, et al. Gout: an independent risk factor for all-cause and cardiovascular mortality. *Rheumatology (Oxford)*. 2010;49(1):141-146. doi:10.1093/rheumatology/kep364.
3. Muller S, Hider SLS, Belcher J, Helliwell T, Mallen CD. Is cancer associated with polymyalgia rheumatica? A cohort study in the General Practice Research Database. *Ann Rheum Dis*. 2014;73(pagination):ate of Pubaton: 10 Ju 2013. doi:10.1136/annrheumdis-2013-203465

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry ☐ *Please specify name and country:*
Academia ☒ *Please specify name and country:* Keele University, UK
Government / NHS ☐ *Please specify name and country:*
Charity ☐ *Please specify name and country:*
Other ☐ *Please specify name and country:*
None ☐

15. Type of Institution conducting the research

Pharmaceutical Industry ☐ *Please specify name and country:*
Academia ☒ *Please specify name and country:* Keele University, UK
Government Department ☐ *Please specify name and country:*
Research Service Provider ☐ *Please specify name and country:*
NHS ☐ *Please specify name and country:*
Other ☐ *Please specify name and country:*

16. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data ☐
The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data** ☒
A data set will be provided by the CPRD[¥€] ☐
CPRD has been commissioned to extract the data and perform the analyses[€] ☐
Other: ☐
If Other, please specify:

17. Primary care data

Please specify which primary care data set(s) are required)
Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐
EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.
Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:
Name of CPRD Researcher Reference number (where available)
Date of contact

SECTION D: INFORMATION ON DATA LINKAGES

18. Does this protocol seek access to linked data

Yes* ☒ No ☐ If No, please move to section E.

19. Please select the source(s) of linked data being requested[§]
[§]Please note: This information will be published on the CPRD's website as part of its transparency policy.

- ☒ ONS Death Registration Data
- ☒ HES Admitted Patient Care
- ☐ HES Outpatient
- ☐ HES Accident and Emergency
- ☐ HES Diagnostic Imaging Dataset
- ☐ MINAP (Myocardial Ischaemia National Aud
- ☐ Cancer Registration Data*
- ☐ PROMS (Patient Reported Outcomes Meas
- ☐ CPRD Mother Baby Link
- ☐ Pregnancy Register

- ☐ Practice Level Index of Multiple Deprivation (Standard)
- ☐ Practice Level Index of Multiple Deprivation (Bespoke)
- ☒ Patient Level Index of Multiple Deprivation***
- ☐ Patient Level Townsend Score ***
- ☐ Other**** *Please specify:*

20. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **<u>not</u>** be included in this count)* 2

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

21. Is linkage to a <u>local[¥]</u> dataset with <1 million patients being requested?
Yes * ☐ No ☒

22. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.
Yes* ☐ No ☒

23. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?
Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

24. Does this protocol describe a purely observational study using CPRD data?
Yes* ☒ No** ☐

25. Does this protocol involve requesting any additional information from GPs?
Yes* ☐ No ☒

26. Does this study require contact with patients in order for them to complete a questionnaire?
Yes* ☐ No ☒

27. Does this study require contact with patients in order to collect a sample?
Yes* ☐ No ☒

SECTION F: DECLARATION

28. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.
- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Dr Alyshah Abdul Sultan Date:21/08/2017 e-Signature (type name): Dr Alyshah Abdul Sultan

PROTOCOL INFORMATION REQUIRED

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title§

§*Please note: This information will be published on CPRD's website as part of its transparency policy*

Polymyalgia rheumatica in primary care: an epidemiological investigation into occurrence and comorbidities.

B. Lay Summary (Max. 200 words)§

Polymyalgia rheumatica (PMR) is a common inflammatory rheumatological condition that affects people over the age of 40. PMR causes stiffness and pain in the shoulders and hips. It has been estimated that approximately 2.43% of women and 1.66% of men will develop PMR in their lifetime and that each year around 8 in every 10,000 people over 40 in the UK develop the condition. Steroid tablets are the main treatment, but some find it difficult to stop taking these medicines. Various studies have been published that suggest that people who have PMR are at an increased risk of developing heart disease, stroke and certain types of blood cancer.

The knowledge of how common PMR is, and which medical conditions may be linked with it, will lead to better diagnosis and treatment of patients with this condition. The first study will update our knowledge of the occurrence of PMR in England and Wales; this was last investigated in a study over 15 years old. Secondly, we will investigate which other medical conditions are more likely to occur in people with PMR before and after their PMR diagnosis, which will help to understand why people find it difficult to stop taking steroids.

C. Technical Summary (Max. 200 words)§

§*Please note: This information will be published on CPRD's website as part of its transparency policy*

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

Polymyalgia rheumatica (PMR) is a common inflammatory rheumatological condition. Treatment involves low dose glucocorticoids, and is generally effective, although some patients have problems with treatment withdrawal.

The risk of developing PMR varies depending on geographic location. The most recent data from the UK, from 1996 to 2002, showed an incidence of 8 per 10,000 per year in people aged over 40 years.

Little is known about comorbidities that may coexist with PMR. This project will 1) re-estimate the incidence and prevalence of PMR in the UK, 2) measure comorbidities before and after PMR diagnosis. For the first aim: incidence rate per 10,000 years, between 1990 and 2017; and point prevalence on 31st March 2017 will be calculated.

For the second, patients with PMR will be individually matched to four controls. Using a nested case-control study, we will calculate the prevalence of individual comorbidities for cases and controls. Odds ratios (OR) and 95% confidence intervals will be obtained using conditional logistic regression. We will then calculate the cumulative probability of each comorbidity up to 10 years after the index date using Kaplan-Meier plots for comorbidities occurring after PMR diagnosis. We will calculate hazard ratios using Cox regression model.

D. Objectives, Specific Aims and Rationale

The overall objective of this project is to use data from the CPRD to quantify the occurrence and comorbidity profile of patients with PMR:

Specific aims

1. To quantify the yearly and average incidence between 1990 and 2017 and point prevalence in March 2017 of PMR in the UK and assess its variation by age, gender, social class, calendar year and geographical region.
2. To measure the frequency of comorbidities before and after PMR diagnosis compared to matched controls.

Rationale

Our current best knowledge of the epidemiology of PMR in the UK comes from a study conducted using data from the General Practice Research Database from 1990 to 2002. (Smeeth, Cook and Hall, 2006) Whilst this study was, at the time, a helpful aid to understanding the burden of PMR, it is now out-of-date. We are a society that is rapidly ageing (Dunnell, 2008) and there are increasing concerns about the health service's ability to cope with the demands of older people with multiple comorbidities. (Moffat and Mercer, 2015) Therefore we propose to update the information regarding the incidence and prevalence of the condition.

In terms of comorbidities, we have conducted a systematic review and identified a number of small scale studies, which provided inconsistent estimates of the association of PMR with various comorbidities. Much of the evidence is focused around autoimmune conditions. Large scale studies exist but only report a limited number of outcomes which does not provide a complete picture of the pattern of comorbidity in people with PMR. Furthermore, previous estimates may be biased, as cases were only recruited from secondary care, yet the majority of patients are managed exclusively in primary care. (Barraclough et al., 2008; Yates et al., 2016) Bringing information about the incidence and prevalence of PMR up to date will lead to a better understanding of the disease burden that PMR causes. Furthermore,

investigating which comorbidities and iatrogenic symptoms that are likely to be present at and following diagnosis, will help to understand the potential 'symptom tail' that has been described in PMR (Mackie et al., 2014)

E. Study Background

Polymyalgia Rheumatica (PMR) is a common inflammatory condition, affecting people over the age of 40. Clinically, PMR is characterised by persisting muscle stiffness, pain and tenderness, predominantly around the neck or shoulder and pelvic girdles. (Salvarani, Cantini and Hunder, 2008) These symptoms are usually accompanied by raised inflammatory markers.

The lifetime risk of developing PMR has been estimated to be approximately 2.43% for women and 1.66% for men. (Crowson et al., 2011) The incidence varies depending on geographic location. The highest incidence has been found in Norway, at 112.6 per 100,000 people; (Gran and Myklebust, 1997) this compares to between 41.3 and 84 per 100,000 in the UK, Denmark and Sweden. (Boesen and Sorensen, 1987; Schaufelberger, Bengtsson and Andersson, 1995; Elling, Olsson and Elling, 1997; Smeeth, Cook and Hall, 2006) The lowest incidence and prevalence, between 12.7 and 18.7 per 100,000 has been demonstrated in southern Europe. (Salvarani et al., 1991; Gonzalez-Gay et al., 1999) The most recent population based incidence and prevalence study (Smeeth, Cook and Hall, 2006) based on UK data is over a decade old. Due to demographic changes in this time, more contemporaneous data are needed to improve planning of health services around disease burden.

Classification criteria for PMR require a patient to be aged over 40 years in order that they are eligible to be diagnosed with PMR. (Dasgupta et al., 2012) Furthermore, it has been demonstrated that PMR is more frequently diagnosed as people age, (Smeeth, Cook and Hall, 2006) as does the risk of developing comorbidities. (Piccirillo et al., 2008) Therefore, the population of patients with PMR may be at high risk of multiple comorbidities. Findings from our systematic review revealed a number of studies that have investigated whether PMR is associated with specific comorbidity(s). These comorbidities include vascular disease, cancer and some neurological and mental health conditions. (B. A. Bengtsson and Malmvall, 1981; Haga et al., 1993; Myklebust et al., 2002; Kremers et al., 2005; Eaton et al., 2006; L A Anderson et al., 2009; Kristinsson et al., 2010; Lanoy and Engels, 2010; Jianguang et al., 2010; Lindqvist et al., 2011; Kang, Sheu and Lin, 2011; Kermani and Warrington, 2011; Li, Sundquist and Sundquist, 2012; Chen et al., 2012; Zoller et al., 2012; Kari Hemminki, Liu, Ji, et al., 2012; M. Fallah et al., 2014; Mahdi Fallah et al., 2014; Muller et al., 2014; Hancock et al., 2014; Pfefiffer et al., 2015; Pujades-Rodriguez et al., 2016; Bellan et al., 2017) However, the results of these studies have been mixed, with some showing increases in certain conditions (e.g. stroke) and others showing no association. Much of the current literature draws on analysis of large Scandinavian health databases and uses standardisation to compare rates of outcomes in those with PMR to the general population. Although large, these studies were unable to take account of the socio-demographic make-up of the population. Other studies (Kremers et al., 2005; Pfefiffer et al., 2015) have been conducted in relatively small samples (e.g. n=193, n= 359).

The majority of previous studies have selected PMR patients from secondary care clinics or from hospital discharge data. As PMR is largely managed in primary care and only a very small minority of patients would be admitted to hospital, these sampling frames are likely to have introduced spectrum bias, making the results less generalisable. Although there is some understanding of the complications caused by

glucocorticoid treatment for PMR, there is currently no clear understanding of what conditions are comorbid with PMR, either before or after diagnosis. We know very little about the wider health of these patients. This study will be the first to look at a comprehensive list of comorbidities in a large group of patients with a matched comparator group. A primary care database study will be the best way of obtaining this data given that an estimated 70% of cases of PMR are dealt with exclusively in primary care. (Yates et al., 2016)

Alongside this, recent work with patient groups has suggested a 'symptom tail' whereby a symptom flare is reported as treatment is withdrawn, further knowledge of the overall health state of these patients may help to understand this phenomenon. This has been referred to in recently released guidelines (Dejaco, Singh, Perel, et al., 2015) which have stated that patients with comorbidities or who are at high risk of relapse be considered for specialist referral and alternative or glucocorticoid sparing therapies However, the guidelines are not specific as to what constitutes these comorbidities or risk factors. This study aims to address this gap.

This study will compare the morbidities in the primary care records of those with PMR to an age, gender and general practice matched control group to assess which morbidities are present before and after PMR diagnosis and how this compares to the general population of this age. By improving our understanding of the comorbidities and iatrogenic symptoms that are likely to be present as glucocorticoid dose for PMR is reduced, this study will help us to understand the potential 'symptom tail' that has been described in PMR. (Mackie et al., 2014)

F. Study Type

The first aim of this study is to describe the prevalence and incidence of PMR in the UK between 1990 and 2017 and look at trends in diagnosis by calendar year. This will be a descriptive study.

The second aim of our study is to consider the association between PMR and other morbidities before and after PMR diagnosis. This will be a hypothesis testing study where our null hypothesis will be that there is no difference in the prevalence/incidence between PMR cases and the general population without PMR.

G. Study Design

The study design chosen will be a retrospective cohort study. We will identify PMR cases from CPRD and a general population comparison group without PMR.

H. Feasibility counts

Based on our feasibility analysis, we anticipate more than 15,000 incident cases of PMR between 1990 and 2010. This will give us enough statistical power to quantify the burden of comorbidities before and after diagnosis.

I. Sample size considerations

The first part of our study (Aim 1) is purely descriptive; therefore no power calculation is necessary.
For our second aim, we will first compare the prevalence of comorbidities between PMR cases and four matched controls. This will give a total sample size of 75,000. We anticipate more than 80% power to detect odds ratio of 1.40 for comorbidities with prevalence of 0.5% (e.g. renal disease) and more than 90% to detect odds ratio

of 1.15 for condition with the overall prevalence of around 5% (e.g. diabetes) in the general population with alpha 0.05.
In terms of looking at comorbidities after PMR diagnosis, we anticipate 8% of controls will consult for relatively common condition such as diabetes over a 10-year period (i.e. 0.8% per annum), as per Kuo et al. (Kuo, 2014) Our sample size will provide 90% power to detect hazard ratio of 1.30. For rare outcomes such as renal disease, with the annual incidence of 0.4%, we will have more than 80% power to detect hazard ratio of 1.4.

J. Data Linkage Required (if applicable):§

§*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

To better ascertain certain comorbidities such as heart disease, cancer cases and mortality, we will utilise Hospital Episode Statistics (HES) and Office of National Statistics (ONS) mortality data. This linkage will form part of our sensitivity analysis.

We may also be able to use HES to identify additional cases that were not identified in CPRD, although the evidence shows that PMR is predominantly diagnosed and managed in primary care. (Barraclough et al., 2008; Yates et al., 2016) However, HES linkage will be useful for identifying comorbidities, particularly those which are managed predominantly in secondary care.

K. Study population

For our first aim, as per Smeeth et al (Smeeth, Cook and Hall, 2006) we will analyse all individuals aged 40 or over registered within CPRD HES between 1990 and 2017. Only acceptable patients contributing data within the up-to-standard (UTS) period will be included. To calculate point prevalence, our denominator will include all registered patients within CPRD who are live and contributing data on 31st March 2017. For our incidence rate analysis, we will only include patients registered within CPRD between 1990 and 2017 with no history of PMR before the study start date. Cases and person-time within the first six months of patients' registration with the practice will be excluded to avoid inclusion of prevalent cases. Incidence will be expressed as per Smeeth et al, (Smeeth, Cook and Hall, 2006) per 10,000 person years. Alongside this, we will present incidence rates by age, gender, social class, calendar year and geographical region.

The study start date will be defined as the latest of: 1st of January 1990, up-to-standard date and patient current registration date. The study end date will be defined as the earliest of 31 of March 2017, transferred out date, date of death and the last date of data collection from practice.

For our second aim, we will restrict our cohort to PMR patients with at least 3 years of continuous registration with a practice prior to their first PMR code. Each patient will be assigned an index date corresponding to the date of their first PMR diagnosis. Those with less than 1 year of follow-up before or after the index date will be excluded.

As part of sensitivity analysis we will look at patients with HES linkage. In these patients, which constitute around 60% of the total population of CPRD, the start date of the study will be 1st April 1997, reflecting when this linkage was established.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

For sensitivity analysis using linked HES data we will amend the study start date to the latest of: patient current registration date + 6 months, the practice up-to-standard date and the start of HES collection- 1st April 1997. The study end date will be defined as the earliest of: practice last collection date, patient deregistration date, study end date and HES last collection date.

L. Selection of comparison group(s) or controls

For our second aim, individuals in the selected sample will each be individually matched to four controls based on year of birth, (± 3 years) sex, general practice and follow-up time (±2 years). Controls will be assigned an 'index' date, which will be the same as the date of their matched PMR case. As with PMR cases, we will exclude controls if they have less than 3 years of follow-up before or less than 1 year of follow-up after index date. In doing this, we are following the same methodology as Kuo et al, (Kuo, 2014) a study into comorbidities in gout performed using CPRD.

M. Exposures, Health Outcomes§ and Covariates

§*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

PMR definition (for Aims 1 and 2): People aged 40 or over who have a first diagnosis of polymyalgia rheumatica entered into their general practice record while registered with a practice contributing to the CPRD during the study period. The Read codes to be used are enclosed in appendix 5. People with a diagnosis of GCA prior to diagnosis of PMR will be included as cases. Furthermore, to be included, cases will have to have received at least two prescriptions for oral glucocorticoids; one within six months of the diagnosis date, with the two prescriptions being within 6 months of each other, used to indicate a clinical response to glucocorticoids. This is following the same methodology of Smeeth et al. (Smeeth, Cook and Hall, 2006)

Outcome (Aim 2): the table in appendix 3 outlines the comorbidities to be included as exposures. These were derived from a combination of three separate processes 1. Review of the Charlson Comorbidity Index, (Charlson et al., 1994) 2. Results from a systematic review, carried out as part of this project, 3. Expert consensus from a group of rheumatologists and GPs experienced in the management of PMR.

The Charlson comorbidity index was chosen as the basic list of comorbidities in a study into comorbidities in gout. (Kuo et al., 2010) As gout and PMR affect a similar age group, it is appropriate to assess for similar comorbidities. This list has been adapted and successfully used with an electronic database which used the ICD 9 classification (Deyo, Cherkin and Ciol, 1992) and subsequently then translated into Read codes for use in UK primary care databases. (Khan et al., 2010) We supplemented this list with comorbidities identified from our systematic review and discussion with experts in the management of PMR.

Our systematic review identified 17,328 unique studies, of which we reviewed 282 abstracts and 155 full text. In total 40 studies were included in narrative synthesis. These included case control, cohort and cross sectional studies which presented original data on comorbidities in PMR.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

For the purpose of this project, we will examine the following comorbidities, where possible, we will stratify these into specific conditions:

- Vascular
- Neurological
- Respiratory
- Rheumatological and Musculoskeletal
- Gastroenterology
- Endocrine
- Renal
- Neoplastic
- Infections
- Psychiatric
- Ophthalmology

Specific conditions that will be included within these headings are tabulated in appendix 3. The Codes list are also given in appendix 5.

As the list of comorbid conditions is quite large and some conditions quite rare, it is anticipated that in some cases there may be small numbers of patients affected. We will aim to aggregate this data into larger groups to increase the likelihood of producing robust data. This will also fulfil a second objective, that of reducing the chance of unintentional (deductive) breaches of patient confidentiality. We also, in keeping with CPRD policy, will not report any cell which contains fewer than five events.

Covariate (aim 2):
For each patient, we will extract information on their smoking status, alcohol consumption and body mass index using the most recent measure before the index date.

N. Data/ Statistical Analysis

Aim 1
We will calculate crude incidence rate of PMR by dividing the total number of new cases by the total person-years of follow-up. We will stratify incidence by age, gender, region, social class (using the patient level index of multiple deprivation) and calendar year. We will use Poisson regression model to assess the impact of covariates (e.g. age, gender) on the incidence of PMR. For each year, we will also calculate age standardised incidence rate and assess trends in incidence rate over time. To calculate point prevalence, we will identify all validated PMR cases (i.e. having received two courses of GC prescriptions within six months of diagnosis) on the 30th of March 2017 (including incidence and prevalent) and divide them by all the patients registered within CPRD who are alive and contributing data on that date. For the cases to be considered part of the prevalence study they will also need to have been prescribed GCs +/- six months around 31st March 2017. As part of sensitivity analysis we will alter this time to assess what effect this has on the prevalence.

We have considered the risk of inaccurate date of diagnosis caused by patients registering with a practice and their prevalent conditions, such as PMR, being recorded as having occurred at the time of registration. To address this, we will investigate the number of times PMR is recorded in the period following current

registration date. Once the incidence has reduced to a steady baseline we will define this as the baseline rate and use this cut off to define the start date of the study.

Aims 2
We will use similar methods used by Kuo. (Kuo, 2014)
We will first calculate the prevalence of individual comorbidities for PMR cases and controls. This will be done by dividing the number of patients with each comorbidity (numerator) by the number of incident PMR cases or matched controls (denominator). We will consider comorbidities ever recorded before the index date. Odds ratios (OR) and 95% confidence intervals will be calculated to examine the association between PMR and previously existing comorbidity using conditional logistic regression. We will adjust our estimates for various sociodemographic and life-style related factors (e.g. age, body mass index (BMI), smoking status, alcohol consumption and socioeconomic status).

For both cases and control, we will then calculate the cumulative probability of each comorbidity up to 10 years after the index date using Kaplan-Meier plots. We will stratify these by individual years after the index date. For those at risk of developing a given comorbidity (not having such comorbidity at index date) we will calculate hazard ratios using Cox regression model. We will adjust our analysis for age, smoking status, BMI and alcohol consumption. The assumption of proportional hazards will be tested using Schoenfeld residuals. We will attempt to take account of the matching in the study design by using a frailty term. However, experience tells us that it can be difficult to get these models to converge due to the flat shape of the likelihood. If convergence is a problem, we will fit the models with robust standard errors, rather than with a frailty term.

To strengthen our findings, we will carry out sensitivity analyses. These analyses will perform two main functions, the first will vary the definition of PMR to ascertain whether this alters the rates of diagnosis of comorbidities found; therefore assessing the validity of the diagnosis of PMR. The second will check how similar HES linked data is to the rest of CPRD.

To address the first aim of the sensitivity analysis, assessing the validity of diagnosis of PMR, we will alter the definition of PMR in the following ways:

1) We will remove the requirement to have GC prescription in order to confirm diagnosis of PMR
2) All patients with PMR who are subsequently diagnosed with a GCA will be excluded (testing the assumption that these patients will have a more severe disease and therefore should not be included as PMR)
3) Excluding all patients who are subsequently diagnosed with conditions which may cause similar symptoms to PMR, such as Rheumatoid arthritis or cancer (again, testing the assumption that these are incorrectly classified as PMR cases).

The second main aim of sensitivity analysis will be to check how similar the HES linked data is to the rest of CPRD. This will involve repeating our analyses on patients with HES link data to assess the impact of hospital data on our estimates and overall conclusions.

O. Plan for addressing confounding

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

Associations of PMR with age and gender are already well-known. Hence matching by these factors will allow some degree of control for any confounding effect they might have. Furthermore, we will also adjust our relative risks for a wide range of covariates including BMI, smoking status, alcohol consumption and social status.

P. Plans for addressing missing data

Based on our previous work, we anticipate that around 25%, 7% and 23% of patients will have missing information on BMI, smoking status and alcohol consumption respectively. These missing data will be considered as a separate category and will be included in our regression model. We do not believe that these data are likely to be missing at random, and therefore we will not use multiple imputation methods.

Q. Patient or user group involvement (if applicable)

The idea for this study originated in work with patients that described a 'symptom tail' in PMR when attempting to withdraw glucocorticoid therapy. Discussions with various stakeholder groups, including the charity PMRGCAuk, have led us to the proposed project.

In order to ensure that a comprehensive list of comorbidities are studied a focus group has been held. This group consisted of local GPs, experienced in managing PMR, together with rheumatologists. They were consulted as to their opinions as to which comorbidities ought to be considered. The combination of professionals from Primary and Secondary Care gave both generalist and specialist perspectives.

The information from this group was further informed by the results of a systematic review into evidence that currently exists on the subject.

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

Results of this study will be published in peer-reviewed journals and presented at appropriate conferences. They will also be disseminated through our local implementation research team and to PMRGCAuk for their members.

S. Limitations of the study design, data sources, and analytic methods

The main limitation to this study involves ensuring the diagnosis of PMR is correct. A set of classification criteria 'for identifying patients appropriate for enrolment into clinical trials of novel medications for the treatment of PMR, and studying long-term outcomes in more homogeneous patient cohorts' has been produced. (Dasgupta et al., 2012) However, these are not explicit diagnostic criteria, furthermore, in this study which will be based on a primary care database it is not practical to ensure all patients have fulfilled these criteria. To improve validity of diagnosis we will ensure that each patient has had at least two glucocorticoid prescriptions in the six months following diagnosis.

Overlapping diagnoses also present a potential limitation, most commonly between GCA and PMR. Around 16-21% of patients with PMR will later develop GCA (Salvarani, Cantini and Hunder, 2008) and around 40-60% of people with GCA will develop PMR (Franzen, Sutinen and Knorring, 1992; C. Salvarani et al., 1995; C

Salvarani et al., 1995; Kermani and Warrington, 2013; Weyand and Goronzy, 2014). These conditions are linked, although GCA is more severe and the pathological processes are separate, we will therefore only assess GCA patients who also have PMR.

Ensuring that we search for all relevant comorbidities. The choice of comorbidities to search for has been partly informed via a focus group including both rheumatologists and GPs with an interest in PMR and also a systematic review into existing literature.

There are a large number of comorbidities within this study, the aim of which is to provide a robust analysis of any comorbidity which may occur in patients with PMR. Where possible we will combine the comorbidities into one of the eleven disease group areas listed previously. To deal with the issue of multiple testing we will strengthen our analysis using a smaller p value to calculate confidence intervals, for example 99%, to reduce the likelihood of false positives being found.

Another potential limitation is under ascertainment of comorbidities. Not all comorbidities will be captured via primary care administration. The risk of this will of course be higher in conditions which are predominantly treated in secondary care such as myocardial infarctions. To assess this risk we perform sensitivity analysis using the HES linkage data.

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Sections which do not apply should be completed as '*Not Applicable*'

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List of Appendices *(Submit all appendices as separate documents to this application)* Appendix 1: 'ISAC CV RP' Dr Partington's CV (new application) Appendix 2: 'TH CV' Dr Helliwell's updated CV Appendix 3: List of comorbidities Appendix 4: 'Steroidcodelist': Oral glucocorticoids code list Appendix 5: 'Read codes for PMR': Code list for PMR and comorbidities code list

APPENDIX 2: List of glucocorticoids used in the analysis

Product code	Name	Active ingredient	Dose
44	Prednisolone 5mg gastro-resistant tablets	Prednisolone	5mg
95	Prednisolone 5mg tablets	Prednisolone	5mg
186	Dexamethasone 500micrograms/5ml oral solution	Dexamethasone	100mcg/ml
229	Cortisone 25mg tablets	Cortisone acetate	25mg
557	Prednisolone 2.5mg gastro-resistant tablets	Prednisolone	2.5mg
578	Prednisolone 1mg tablets	Prednisolone	1mg
955	Prednisolone 5mg soluble tablets	Prednisolone	5mg
1063	Prednisolone sodium phosphate	Prednisolone	5mg
1280	Dexamethasone 2mg tablets	Dexamethasone	2mg
1709	Hydrocortisone pellets 2.5 mg loz		
1971	Betnesol 500microgram soluble tablets	Betamethasone sodium phosphate	500mcg
2044	PREDNISONE 2.5 MG TAB		
2130	Methylprednisolone 4mg tablets	Methylpred-nisolone	4mg
2368	Prednisolone 2.5mg tablet	Prednisolone	2.5mg
2390	PREDNISOLONE E/C 1 MG TAB		
2704	Prednisolone 25mg tablets	Prednisolone	25mg
2799	PREDNISOLONE 10 MG TAB		
2949	Prednisone 5mg tablets	Prednisone	5mg
3059	PREDNISOLONE 50 MG TAB		
3345	Sintisone Tablet	Prednisolone Steaglate	
3418	Hydrocortisone 10mg tablets	Hydrocortisone	10mg
3543	Chloramphenicol & hydrocortisone oint eye		
3557	Prednisone 1mg tablets	Prednisone	1mg
3969	DEXAMETHASONE 8 MG TAB		
3992	Deflazacort 6mg tablets	Deflazacort	6mg
4535	Hydrocortisone 20mg tablets	Hydrocortisone	20mg
4779	Dexamethasone 500microgram tablets	Dexamethasone	500mcg
4943	Dexamethasone 2mg/5ml oral solution sugar free	Dexamethasone	400mcg/1ml
5157	Dexamethasone 2mg/5ml oral solution	Dexamethasone	2mg/5ml
5490	Deltacortril 5mg gastro-resistant tablets	Prednisolone	5mg
5913	Deltacortril 2.5mg gastro-resistant tablets	Prednisolone	2.5mg
6098	Hydrocortone 10mg tablets	Hydrocortisone	10mg
7286	Betamethasone 500microgram soluble tablets sugar free	Betamethasone	500mcg
7548	Cortisone 5mg capsules	Cortisone acetate	5mg
7584	PREDNISOLONE 4 MG TAB		
7710	PREDNISOLONE 15 MG TAB		
7934	PREDNISONE 30 MG TAB		
8261	Medrone 16mg tablets	Methylpred-nisolone	16mg

Product code	Name	Active ingredient	Dose
9375	Deflazacort 1mg tablets	Deflazacort	1mg
9727	Prednisolone 50mg tablets	Prednisolone	50mg
9994	Decadron 500microgram tablets	Dexamethasone	500mcg
10552	Methylprednisolone 16mg tablets	Methylpred-nisolone	16mg
10574	Cortisone acetate 5mg tablets	Cortisone Acetate	5mg
10683	Medrone 2mg tablets	Methylpred-nisolone	2mg
10684	Methylprednisolone 2mg tablets	Methylpred-nisolone	2mg
10754	Hydrocortistab 20mg Tablet	Hydrocortisone	20mg
10864	Betamethasone 500microgram tablets	Betamethasone	500mcg
11149	Betnelan 500microgram tablets	Betamethasone	500mcg
12398	Cortelan 25mg Tablet	Cortisone acetate	25mg
12400	Cortisyl 25mg Tablet	Cortisone acetate	25mg
13043	Hydrocortone 20mg tablets	Hydrocortisone	20mg
13522	PREDNISOLONE 2 MG TAB		
13615	PREDNISONE 10 MG TAB		
14076	Hydrocortisone 5mg/5ml Oral solution	Hydrocortisone	5mg/5ml
14172	Methylprednisolone 100mg tablets	Methylpred-nisolone	100mg
15471	HYDROCORTISONE 25 MG TAB		
15555	Medrone 4mg tablets	Methylpred-nisolone	4mg
15617	Ledercort 4mg Tablet	Triamcinolone Acetonide	4mg
16724	PREDNISONE 50 MG TAB		
17101	DEXAMETHASONE 750 MCG TAB		
17410	Deflazacort 30mg tablets	Deflazacort	30mg
18042	Medrone 100mg tablets	Methylpred-nisolone	100mg
18637	Cortistab 25mg Tablet	Cortisone acetate	25mg
19141	Prednisolone 5mg soluble tablets	Prednisolone	5mg
19908	Triamcinolone 2mg Tablet	Triamcinolone Acetonide	2mg
20095	Precortisyl forte 25mg Tablet	Prednisolone	25mg
20577	Calcort 6mg Tablet	Deflazacort	6mg
20670	PREDNISOLONE E/C		
21218	Dexsol 2mg/5ml oral solution	Dexamethasone	400mcg/ml
21417	Prednisolone 5mg tablets	Prednisolone	5mg
21465	BETAMETHASONE .1 MG TAB		
21833	Decortisyl 5mg Tablet	Prednisone	5mg
21903	Oradexon-organon 2mg Tablet	Dexamethasone	2mg
22555	Calcort 1mg tablets	Deflazacort	1mg
22827	BETAMETHASONE .1 MG		
22894	HYDROCORTISONE 4 MG		

Product code	Name	Active ingredient	Dose
23111	Triamcinolone 4mg Tablet	Triamcinolone Acetonide	4mg
23210	Cortistab 5mg Tablet	Cortisone Acetate	5mg
23512	Precortisyl 5mg Tablet	Prednisolone	5mg
24014	Ledercort 2mg Tablet	Triamcinolone Acetonide	2mg
24716	PREDNISOLONE E/C		
25272	Precortisyl 1mg Tablet	Prednisolone	1mg
27083	BETAMETHASONE VALERATE .1 MG TAB		
27889	PREDNISOLONE		
27959	PREDNISOLONE		
27962	Deltastab 1mg Tablet	Prednisolone	1mg
28375	Prednisolone 2.5mg gastro-resistant tablets	Prednisolone	2.5mg
28376	Prednisolone 2.5mg Gastro-resistant tablet	Prednisolone	2.5mg
28859	Deltastab 5mg Tablet	Prednisolone	5mg
29112	Calcort 30mg tablets	Deflazacort	30mg
29333	Prednisolone 5mg tablets	Prednisolone	5mg
31327	Prednisolone steaglate 6.65mg tablet	Prednisolone Steaglate	6.65mg
31532	Prednisolone 5mg gastro-resistant tablets	Prednisolone	5mg
32803	Prednisolone 5mg gastro-resistant tablets	Prednisolone	5mg
32835	Prednisolone 5mg tablets	Prednisolone	5mg
33691	Prednisolone 5mg Gastro-resistant tablet	Prednisolone	5mg
33988	Prednisolone 5mg Tablet	Prednisolone	5mg
33990	Prednisolone 5mg Tablet	Prednisolone	5mg
34109	Prednisolone 5 mg gastro-resistant tablet	Prednisolone	5mg
34393	Prednisolone 5mg gastro-resistant tablets	Prednisolone	5mg
34404	Prednisolone 1mg tablets	Prednisolone	1mg
34452	Prednisolone 1mg tablets	Prednisolone	1mg
34461	Prednisolone 2.5mg gastro-resistant tablets	Prednisolone	2.5mg
34631	Prednisolone 1mg Tablet	Prednisolone	1mg
34660	Prednisolone 1mg tablets	Prednisolone	1mg
34748	Prednisolone 1mg tablets	Prednisolone	1mg
34781	Prednisolone 5mg tablets	Prednisolone	5mg
34801	Dexamethasone 0.5mg/5ml Oral solution	Dexamethasone	100mcg/ml
34880	Dexamethasone 2mg tablets	Dexamethasone	2mg
34914	Prednisolone 1mg Tablet	Prednisolone	1mg
34915	Dexamethasone 500microgram tablets	Dexamethasone	500mcg
34978	Prednisolone 1mg tablets	Prednisolone	1mg
36055	Dexamethasone 2mg Tablet	Dexamethasone	2mg
38022	Hydrocortisone 10mg/5ml oral suspension	Hydrocortisone	2mg/1ml
38054	Hydrocortisone Tablet	Hydrocortisone	
38407	Prednisolone 20mg tablet	Prednisolone	20mg
41335	Calcort 6mg tablets	Deflazacort	6mg
41515	Prednisolone 5mg tablets	Prednisolone	5mg
41745	Prednisolone 25mg tablets	Prednisolone	25mg

Product code	Name	Active ingredient	Dose
43544	Prednisone 5mg Tablet	Prednisone	5mg
44380	Prednisone 1mg modified-release tablets	Prednisone	1mg
44723	Prednisone 5mg modified-release tablets	Prednisone	5mg
44802	Lodotra 5mg modified-release tablets	Prednisone	5mg
44803	Lodotra 2mg modified-release tablets	Prednisone	2mg
45234	Dexamethasone 100microgram capsules	Dexamethasone	100mcg
45302	Prednisolone 5mg Tablet	Prednisolone	5mg
46711	Prednisone 2mg modified-release tablets	Prednisone	2mg
47142	Prednisolone 5mg Soluble tablet	Prednisolone	5mg
50225	Betnesol 500microgram soluble tablets	Betamethasone	500mcg
51722	Hydrocortisone 5mg/5ml oral suspension	Hydrocortisone	1mg/1ml
51753	Prednisolone 1mg tablets	Prednisolone	1mg
51824	Hydrocortisone 5mg/5ml oral suspension sugar free	Hydrocortisone	1mg/1ml
51849	Hydrocortisone 1mg/5ml oral suspension		
51871	Hydrocortisone 2mg capsules		
51872	Hydrocortisone 2.5mg capsules	Hydrocortisone	2.5mg
52053	Hydrocortisone 3mg/5ml oral suspension		
52396	Dexamethasone 1mg/5ml oral solution	Dexamethasone	200mcg/ml
53143	Cortisone 25mg tablets	Cortisone acetate	25mg
53207	Dexamethasone tablets	Dexamethasone	
53313	Prednisolone 20mg/5ml oral suspension	Prednisolone	4mg/1ml
53336	Prednisolone 25mg tablets	Prednisolone	25mg
53705	Cortisone acetate 5mg Capsule	Cortisone acetate	5mg
54118	Prednisolone 25mg/5ml oral suspension	Prednisolone	5mg/1ml
54432	Lodotra 1mg modified-release tablets	Prednisone	1mg
54434	Prednisolone 2.5mg/5ml oral suspension	Prednisolone	500mcg/ml
54793	Dexamethasone 2mg/5ml oral suspension	Dexamethasone	400mcg/ml
54794	Hydrocortisone 20mg modified-release tablets		
55024	Prednisolone 5mg/5ml oral solution	Prednisolone	1mg/1ml
55401	Dexamethasone 500microgram tablets	Dexamethasone	500mcg
55480	Prednisolone 2.5mg gastro-resistant tablets	Prednisolone	2.5mg
56347	Dexamethasone 5mg/5ml oral solution	Dexamethasone	1mg/1ml
56443	Dexamethasone 10mg/5ml oral solution		
56891	Prednisolone 1mg tablets	Prednisolone	1mg
57931	Hydrocortisone 20mg tablets	Hydrocortisone	20mg
58000	Prednisolone 5mg tablets	Prednisolone	5mg
58234	Prednisolone 10mg/5ml oral solution	Prednisolone	2mg/1ml
58369	Prednisolone 5mg tablets	Prednisolone	5mg
58384	Prednisolone 1mg tablets	Prednisolone	1mg
58987	Prednisolone 5mg gastro-resistant tablets	Prednisolone	5mg
59229	Dilacort 5mg gastro-resistant tablets	Prednisolone	5mg
59283	Dilacort 2.5mg gastro-resistant tablets	Prednisolone	2.5mg
59338	Prednisolone 1mg/5ml oral solution	Prednisolone	200mcg/ml
59912	Prednisolone 5mg gastro-resistant tablets	Prednisolone	5mg
60120	Dexamethasone 2mg tablets	Dexamethasone	2mg

Product code	Name	Active ingredient	Dose
60421	Prednisolone 5mg tablets	Prednisolone	5mg
61132	Prednisolone 1mg tablets	Prednisolone	1mg
61162	Prednisolone 5mg tablets	Prednisolone	5mg
62909	Dexamethasone 2mg tablets	Dexamethasone	2mg
63066	Prednisolone 2.5mg tablets	Prednisolone	2.5mg
63549	Prednisolone 1mg/ml oral solution	Prednisolone	1mg/1ml
64007	Pevanti 10mg tablets	Prednisolone	10mg
64008	Pevanti 2.5mg tablets	Prednisolone	2.5mg
64059	Hydrocortisone 2.5mg/5ml oral suspension	Hydrocortisone	500mcg/ml
64128	Pevanti 5mg tablets	Prednisolone	5mg
64221	Prednisolone 5mg/5ml oral suspension	Prednisolone	1mg/1ml
64787	Hydrocortisone 10mg tablets	Hydrocortisone	10mg
65626	Prednisolone 10mg/5ml oral suspension	Prednisolone	2mg/1ml
65984	Hydrocortisone 10mg tablets	Hydrocortisone	10mg
66327	Hydrocortisone 20mg tablets	Hydrocortisone	20mg
66550	Prednisolone 5mg gastro-resistant tablets	Prednisolone	5mg
66666	Hydrocortisone 10mg tablets	Hydrocortisone	10mg
67107	Prednisolone 5mg gastro-resistant tablets	Prednisolone	5mg
67559	Prednisolone 5mg/5ml oral solution unit dose	Prednisolone	1mg/1ml
68182	Dexamethasone 2mg tablets	Dexamethasone	2mg
68489	Dexamethasone 4mg tablets	Dexamethasone	4mg
68497	Prednisolone 2.5mg gastro-resistant tablets	Prednisolone	2.5mg
68593	Dexamethasone 5mg/5ml oral suspension	Dexamethasone	1mg/1ml
69568	Dilacort 5mg gastro-resistant tablets	Prednisolone	5mg
69572	Dexamethasone 4mg/5ml oral suspension	Dexamethasone	800mcg/ml
69686	Pevanti 25mg tablets	Prednisolone	25mg

Clinical and epidemiological research

EXTENDED REPORT

Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study

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ABSTRACT

Objective Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease in older people. Contemporary estimates of the incidence and prevalence are lacking, and no previous study has assessed treatment patterns at a population level. This study aims to address this.

Methods We extracted anonymised electronic medical records of patients over the age of 40 years from the Clinical Practice Research Datalink in the period 1990–2016. The absolute rate of PMR per 100 000 person-years was calculated and stratified by age, gender and calendar year. Incidence rate ratios were calculated using a Poisson regression model. Among persons with PMR, continuous and total duration of treatment with glucocorticoids (GC) were assessed.

Results 5 364 005 patients were included who contributed 44 million person-years of follow-up. 42 125 people had an incident diagnosis of PMR during the period. The overall incidence rate of PMR was 95.9 per 100 000 (95% CI 94.9 to 96.8). The incidence of PMR was highest in women, older age groups and those living in the South of England. Incidence appears stable over time. The prevalence of PMR in 2015 was 0.85 %. The median (IQR) continuous GC treatment duration was 15.8 (7.9–31.2) months. However, around 25% of patients received more than 4 years in total of GC therapy.

Conclusions The incidence rates of PMR have stabilised. This is the first population-based study to confirm that a significant number of patients with PMR receive prolonged treatment with GC, which can carry significant risks. The early identification of these patients should be a priority in future research.

Key messages

What is already known about this subject?
- The most recent large scale population estimates of the incidence and prevalence of polymyalgia rheumatica were published in 2006 and no similar sized estimates exist of the duration of glucocorticoid treatment in patients with this condition.

What does this study add?
- This study confirms that the incidence of polymyalgia rheumatica has stabilised since the turn of the century and finds that a significant proportion of patients remain on glucorticoid treatment for much longer than guidelines suggest.

How might this impact on clinical practice or future developments?
- These findings will prompt further work to identify those at risk of prolonged glucocorticoid treatment and its inherent risks.

INTRODUCTION

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease affecting older people. Its impact on patients' lives can be devastating, causing stiffness, severe pain and significant impairment to daily activities.[1] Glucocorticoids (GCs) remain the mainstay of treatment.[2]

The incidence and prevalence of PMR vary depending on geography; as latitude increases, so do PMR rates.[3] Previous studies have estimated the prevalence of PMR to lie between 0.1% and 1%[4 5] and the incidence between 12 and 113 per 100 000 person-years.[6–8] The majority of cases of PMR are treated in primary care (71%–84%)[7 9]; however, much of the existing literature is based on secondary care hospital records. Therefore the burden of disease may have been underestimated. One large study (Smeeth *et al*[10]) used primary care data to estimate the incidence of PMR, reporting an overall rate of 84 per 100 000 person-years, which was increasing with time. However, the final year of data published in this study was 2001; therefore, more contemporaneous estimates of national data are needed to guide health service provision.

PMR is managed with gradually reducing GC therapy, from moderate to low doses.[3] Joint guidance released by the American College of Rheumatology and the European League Against Rheumatism advises GC treatment for most patients with PMR should end by 2 years.[2] However, it has been suggested a large proportion of patients experience symptom flare on cessation, or even reduction, of GC therapy (a 'symptom tail').[11]

The aims of this study are to quantify the overall incidence and prevalence of PMR in the UK using a large population-based database and to investigate prescribing of GCs in those diagnosed with PMR.

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METHODS

Data source and study population

Almost all healthcare in the UK is delivered by the National Health Service (NHS), a public system funded by taxation that provides free, or low-cost, healthcare to all residents. Around 90% of patient contacts in the UK with the NHS is via primary care,[12] and 98% of people who live in the UK are registered with a general practice. We used data from the Clinical Practice Research Datalink (CPRD; July 2017 version), which contains data for around 17 million contributing patients within 718 (7.5% of the total) UK general practices. This database, containing electronic, coded information collected during the course of routine healthcare, is representative of the UK population in terms of age, sex and ethnicity,[13] and has been used extensively for primary care research.

Incidence

We analysed data collected between 1 January 1990 and 1 January 2016. Patients contributed data after the latest of four events: (1) the study start date, (2) the date at which they became 40 years old, (3) the date they registered at a participating practice plus 6 months, or (4) the date at which the practice was adjudged to reach internal quality standards, known as the 'up-to-standard' date.

The date at which each follow-up ended was the earliest of five events: (1) the end of study period (1 January 2016), (2) the date when a patient transferred out of a practice, (3) the date of death, (4) the last date of data collection from the practice or (5) the date when they were diagnosed with PMR.

Patients with a Read-coded diagnosis of PMR (codes: N20.00 Polymyalgia rheumatica, N200.00 Giant cell arteritis with polymyalgia rheumatica) in their general practice record were included as incident cases. The first 6 months following registration with a practice were excluded from the incidence analysis to avoid inclusion of prevalent cases which may have been incorrectly recorded at the point of registration.[10] To improve case ascertainment, we only considered PMR diagnosis to be valid if patients received at least two prescriptions for oral GCs: one within 6 months of the diagnosis date and the second within 6 months of the first prescription.[10] Patients could have a diagnosis of both PMR and giant cell arteritis (GCA). We looked only at the first occurrence of PMR; therefore, all subsequent person-time and diagnostic codes were excluded. This process is summarised in online supplementary figure 1.

Treatment of PMR

To ascertain trends in the management of PMR, we assessed patterns of GC prescribing in the incident cases of PMR. All GC prescriptions recorded in CPRD using medications from the British National Formulary (BNF) chapter 6.3.2 'Glucocorticoid therapy' were included.[14] CPRD contains information about the quantity of medication prescribed, the number of units of medication to be taken each day and the prescription duration. The algorithm used to define duration and dose of GC therapy (detailed in online supplementary figure 2) has been defined elsewhere.[15] Kaplan-Meier survival methods were used to calculate the median duration of time from diagnosis until completion of continuous GC therapy. The end of a treatment course was determined to have occurred when no further GC prescriptions occurred for 90 days after the calculated duration of the previous prescription. Patients were censored if they were lost to follow-up prior to stopping treatment. The 90-day period was chosen as it is the same as in previous CPRD-based studies of medication use.[16] As part of a sensitivity analysis, we recalculated this duration (1) by increasing the interval between prescriptions to 6 months; or (2) in patients who received a diagnosis with another rheumatological condition either prior to PMR diagnosis or in the 2 years subsequently; or (3) were referred to secondary care rheumatology services.

Statistical analysis

Crude incidence rates of PMR were calculated by dividing the total number of new cases by the total person-years of follow-up per 100 000 person-years. Incidence rates were stratified by age, gender, region and calendar year. Patient age was grouped into decades. Lexis expansion[17] was used to calculate incidence rates by year following the study start date of 1 January 1990.

To compare the absolute rate of PMR by patient characteristics, we used a Poisson regression model and calculated the incidence rate ratios (IRR) for each covariate, including sex, age, region and calendar year of diagnosis. Age-adjusted incidences for each covariate were calculated with direct standardisation, using the sample population structure over the whole study.

For treatment pattern analysis, we calculated the average daily and total dose of GC prescribed, as well as the cumulative treatment time and the total number of prescriptions and separate treatment courses each patient received. Dosage calculations were made by converting the strength of all medications to milligrams of prednisolone equivalent using the BNF conversion tables of equivalent anti-inflammatory doses.[14] Results were stratified by starting GC dose, age and sex.

Point prevalence of PMR was calculated for each calendar year by dividing the total number of patients who have received a diagnosis of PMR at any time in the past and were alive and contributing data on 31 December of that year (numerator) by the total number of patients alive and contributing data on that date (denominator), thereby including incident and prevalent cases. As part of sensitivity analysis, we recalculated the prevalence in patients aged over 55 years in order to compare with a recent study.[9] Statistical analyses were conducted using Stata V.15.1.

RESULTS

Overall incidence

A total of 5 364 005 individuals contributed 43.97 million person-years of follow-up in the period 1990–2016. The total number of new occurrences of PMR that fulfilled the GC prescription criteria was 42 145. This equated to 90.4% of the total number of PMR cases recorded during this time. The overall incidence rate of PMR among patients aged 40 years and over was 95.9 (95% CI 94.9 to 96.8) per 100 000 person-years (table 1). The incidence rates were significantly higher at older ages: those aged >70 years were around 10 times (IRR=9.61 (95% CI 9.25 to 9.98)) more likely to have PMR compared with those between the ages of 50 and 59 years. Women were 67% more likely to develop PMR compared with men (IRR=1.67 (95% CI 1.64 to 1.71)). A marked variation in incidence rates by region was found (figure 1), with rates highest in the south-west region of the UK (124.1 (95% CI 120.6 to 127.6)) and lowest in the north-east (65 (95% CI 59.5 to 70.9)).

Incidence of PMR over time

The variation in incidence rates of PMR over time is displayed in table 2 and figure 2. The rate of diagnosis of PMR dipped a little after 1990 until 1996 before increasing significantly until just after the end of the last century; after this the rate of diagnosis of PMR remained relatively stable between 2003 and 2014.

GC prescribing in PMR

In total 1 242 841 GC prescriptions were issued to patients after a diagnosis with PMR; of these 99.9% contained

Table 1 Incidence rates of polymyalgia rheumatica, with incidence rate ratios, stratified by age, sex and region

	Events (n)	Person-time at risk (100 000 years)	Rate per 100 000 (95% CI)	Incidence rate ratio (95% CI)*	Age-standardised incidence rate† (per 100 000 person-years)
Overall	42 145	439.70	95.9 (94.9 to 96.8)		
Age					
40–49	409	129.96	3.2 (2.9 to 3.47)	0.11 (0.10 to 0.13)	
50–59	3139	113.75	27.6 (26.7 to 28.6)	Reference	
60–69	9683	91.62	105.7 (103.6 to 107.8)	3.80 (3.65 to 3.96)	
70–79	17 620	64.76	272.1 (268.1 to 276.1)	9.61 (9.25 to 9.98)	
80+	10 405	33.05	314.9 (308.9 to 321)	10.58 (10.17 to 11.13)	
Sex					
Male	13 651	212.06	64.4 (63.3 to 65.5)	Reference	69.22
Female	28 494	227.64	125.2 (123.7 to 126.6)	1.67 (1.64 to 1.71)	114.87
Region					
North East	500	7.69	65 (59.5 to 70.9)	0.82 (0.75 to 0.90)	62.54
North West	3843	49.36	77.9 (75.4 to 80.4)	Reference	77.54
Yorkshire and the Humber	1286	16.91	76.1 (72.0 to 80.3)	0.97 (0.92 to 1.04)	73.62
East Midlands	1461	16.71	87.4 (83.1 to 92.0)	1.14 (1.07 to 1.21)	86.13
West Midlands	4207	41.45	101.5 (98.5 to 104.6)	1.26 (1.21 to 1.32)	98.44
East of England	4698	38.44	122.2 (118.8 to 125.8)	1.56 (1.49 to 1.62)	120.41
South West	4850	39.10	124.1 (120.6 to 127.6)	1.45 (1.39 to 1.51)	112.96
South Central	4754	46.70	101.8 (98.9 to 104.7)	1.29 (1.24 to 1.35)	101.57
London	2901	40.63	71.4 (68.9 to 74.1)	0.97 (0.93 to 1.02)	75.76
South East Coast	5167	43.89	117.7 (114.6 to 121)	1.42 (1.36 to 1.48)	110.23
Northern Ireland	991	13.76	72 (67.7 to 76.6)	0.93 (0.87 to 1.00)	73.06
Scotland	3154	40.05	78.7 (76.0 to 81.5)	1.03 (0.99 to 1.08)	81.51
Wales	4333	45.01	96.3 (93.5 to 99.2)	1.16 (1.11 to 1.21)	90.05

*Adjusted for age, sex, region and year of diagnosis if not stratified as a covariate.
†Incidence rate is adjusted by age using overall proportion of person-time contributed per 10-year age category.

information about quantity of medication prescribed and 48.3% about numeric daily dose. The median time taken for patients to stop continuous therapy was 1.31 years (IQR 0.65–2.6) (figure 3). When the treatment gap was increased to 6 months, this increased to 1.88 years (0.93–4.00). When the total GC treatment time was reviewed, the median duration increased further to 1.93 years (0.95–4.03), meaning around 25% of patients received more than 4 years of therapy. Among patients with a rheumatology diagnosis, or those referred to rheumatology, the median continual duration of GC therapy was greater at 1.49 (IQR 0.73–3.16) and 1.55 (IQR 0.79–3.06) years, respectively. The median first and average daily doses of GC received (in milligrams of prednisolone equivalent) were 15 mg (IQR 8–21) and 6 mg (IQR 4–9), respectively. However, 7138 (16.9%) patients received on average greater than 10 mg GC per day. The median total dose of GC received (in grams of prednisolone equivalent) was 4 g (IQR 2–8). Repeating analyses stratified by initial GC dose, age and sex were unremarkable, with only patients aged under 50 receiving significantly fewer prescriptions.

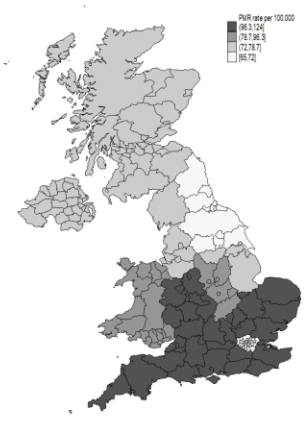

Figure 1 Incidence rates of polymyalgia rheumatica (PMR) by region, 1990–2015.

Prevalence of PMR

The point prevalence of PMR in 2015 among patients aged over 40 years was 0.85% (table 2) and was markedly different between men and women (0.6% and 1.16%). The prevalence increased to 1.7% (95% CI 1.69% to 1.71%) in patients aged over 55 years.

DISCUSSION

Main findings

This study estimates the burden of PMR in the UK to be slightly higher than previously estimated. In 2015 around 1 in 120 adults aged over 40 have received a diagnosis of PMR. Overall, the incidence of PMR during the study period 1990–2016 was 95.9 per 100 000 person-years (95% CI 94.9 to 96.8). However, after increasing until 2002, the incidence rate of PMR has stabilised. Almost 50% of patients with PMR received more than 2 years

Table 2 Incidence rates of polymyalgia rheumatica by calendar year

Year	Events (n)	Person-years at risk per 100 000	Rate per 100 000 (95% CI)	Incidence Rate Ratio (95% CI)*	Age-standardised incidence rate†	Point prevalence (%)
Overall	42 145	439.70	95.9 (94.9 to 96.8)			0.84
1990	261	3.30	79.2 (70.1 to 89.4)	Reference	76.3	0.34
1991	336	4.54	74 (66.5 to 82.3)	0.91 (0.77 to 1.07)	69.4	0.38
1992	401	5.27	76.1 (69 to 83.9)	0.94 (0.80 to 1.09)	72.1	0.44
1993	464	6.02	77.1 (70.4 to 84.4)	0.95 (0.81 to 1.10)	71.9	0.49
1994	476	6.55	72.7 (66.5 to 79.6)	0.90 (0.77 to 1.04)	68.4	0.52
1995	548	7.06	77.7 (71.4 to 84.4)	0.96 (0.83 to 1.11)	74	0.57
1996	657	8.06	81.5 (75.5 to 88)	1.01 (0.87 to 1.16)	77.4	0.60
1997	754	9.34	80.7 (75.2 to 86.7)	1.01 (0.88 to 1.17)	77.6	0.62
1998	863	10.69	80.7 (75.5 to 86.3)	1.01 (0.88 to 1.16)	76.5	0.64
1999	1239	13.00	95.3 (90.1 to 100.8)	1.20 (1.05 to 1.38)	91.7	0.66
2000	1537	15.85	96.9 (92.2 to 101.9)	1.23 (1.08 to 1.40)	93.7	0.68
2001	1792	17.75	100.9 (96.4 to 105.7)	1.28 (1.13 to 1.46)	98.1	0.71
2002	2131	20.05	106.3 (101.9 to 110.9)	1.36 (1.20 to 1.55)	103.5	0.74
2003	2211	21.49	102.9 (98.7 to 107.3)	1.33 (1.17 to 1.51)	101.4	0.77
2004	2296	22.96	100 (96 to 104.2)	1.30 (1.15 to 1.48)	98.5	0.79
2005	2348	23.73	99 (95 to 103)	1.30 (1.14 to 1.48)	98	0.80
2006	2389	24.12	99.1 (95.2 to 103.1)	1.30 (1.15 to 1.48)	97.7	0.83
2007	2451	24.45	100.3 (96.4 to 104.3)	1.32 (1.16 to 1.50)	99.7	0.83
2008	2495	24.60	101.4 (97.5 to 105.5)	1.33 (1.17 to 1.51)	100.7	0.85
2009	2447	24.64	99.3 (95.5 to 103.3)	1.30 (1.15 to 1.48)	98.2	0.85
2010	2497	24.34	102.6 (98.6 to 106.7)	1.35 (1.19 to 1.53)	101.6	0.86
2011	2379	23.83	99.8 (95.9 to 103.9)	1.32 (1.16 to 1.50)	99.1	0.87
2012	2268	23.50	96.5 (92.6 to 100.6)	1.28 (1.12 to 1.45)	95.9	0.87
2013	2198	22.51	97.6 (93.6 to 101.8)	1.29 (1.14 to 1.47)	96.8	0.88
2014	2037	20.58	99 (94.8 to 103.4)	1.30 (1.14 to 1.48)	97.2	0.88
2015	1603	17.60	91.1 (86.7 to 95.6)	1.20 (1.05 to 1.36)	89.1	0.85

*Adjusted for region, age and gender.
†Incidence rate is adjusted by age using overall proportion of person-time contributed per 10-year age category.

of GC therapy following diagnosis, despite guidelines suggesting treatment should have ended.

Strengths and limitations

We have conducted the largest study yet to calculate a true estimate of the current incidence, prevalence and real-world treatment patterns of patients with PMR. This study uses robust methodology in a large, established database of patients who are representative of the UK population. It therefore is likely to be an accurate estimate of the true burden of PMR. Most patients with PMR are managed exclusively in primary care[7 9]; therefore, this is the most appropriate setting to conduct this study.

A potential limitation is the ascertainment of cases. This was based on medical codes recorded by the primary care physicians, rather than research classification criteria,[18] as there is no sufficient detail in medical records and therefore CPRD to allow this. Patients may therefore subsequently be diagnosed with an alternative condition. However, using GC prescriptions to confirm PMR diagnosis is well established.[10 19] Greater than 90% of patients with a diagnosis of PMR received at least two GC prescriptions, showing the diagnosis is likely to be accurate in the vast majority of patients. Furthermore, in the UK diagnoses made in secondary care are communicated to, and recorded in, primary care. Therefore although this study examined patients in primary care, it will also contain information from secondary care.

Comparison with other studies

The highest incidence, 113 per 100 000 patients, previously reported was a study from the South West of England.[4] Although the overall incidence rate we found is lower than this, our estimate for this region was slightly higher (124.1 (120.6, 127.6)). In the USA, the most recent estimate of PMR rate reported by Raheel *et al*[8] was 63.9 per 100 000. This is lower than our figure. However, this study was not conducted in primary care, and stricter diagnostic criteria rather than codes were used.[20] We included patients from a much larger sample, and while our PMR definition is not ideal our estimates are broadly in line with other studies that have used clinical classification criteria. Therefore we believe that the risk of misclassification is minimal.

Women were more likely to develop PMR, with a female to male ratio of approximately 2:1, reflecting previous studies.[10] The strong association between older age and risk of developing PMR has been demonstrated before, with other studies reporting a median age at diagnosis of 70[9] or 75 years.[7] As rates of frailty, aches, pains[21] and erythrocyte sedimentation rate (ESR) measurements[22] increase with age, it is possible that primary care physicians may overdiagnose PMR in at least some of these patients.

The prevalence of PMR has been found to vary between 0.1% and 1% in North Europe and North America.[4 23] The prevalence of 0.85% in 2015 calculated in our study is consistent with this. In a recent study in a single large GP practice in the south of the UK, Yates *et al*[9] reported a prevalence of 2.27% in those aged

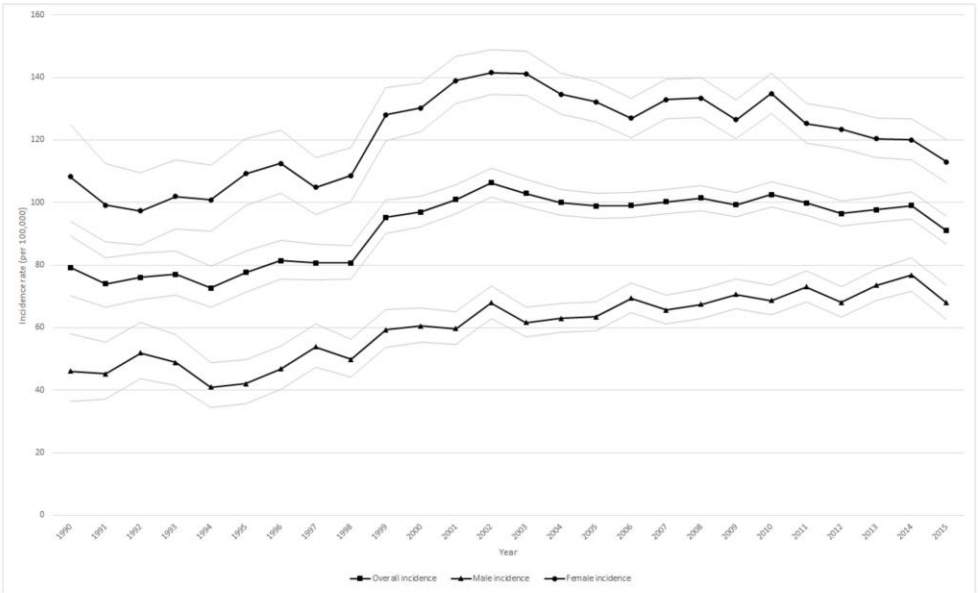

Figure 2 Overall, male and female incidence of polymyalgia rheumatica, with 95% CI, 1990–2015.

55 years and over. In our data, the prevalence in this group was 1.7%. This discrepancy could be explained by the higher incidence of PMR in the south and east of the UK.

Given PMR is known to preferentially affect people of Northern European descent, these results are likely to be generalisable to countries with significant number of people from this ethnic group. However, the incidence and prevalence figures reported in this study are less generalisable to countries at lower latitudes, as incidence and prevalence rates have been found to reduce with decreasing latitude.[5 24 25]

The incidence of PMR appears higher in the south of the UK compared with the north. This was also demonstrated by Smeeth

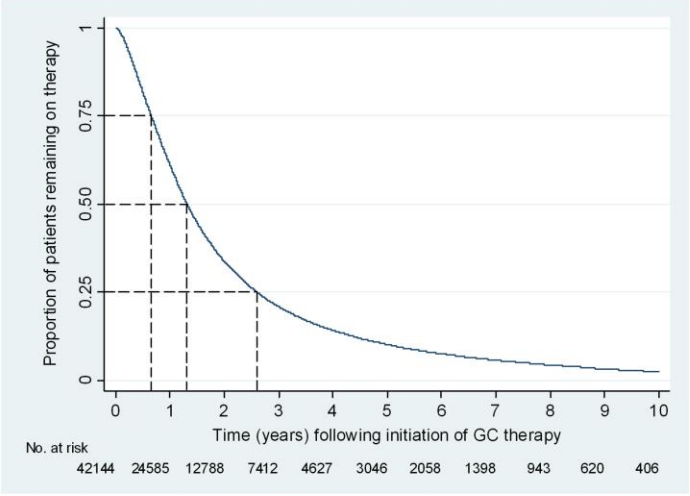

Figure 3 Kaplan-Meier plot showing time to final glucocorticoid (GC) prescription, defined as a gap of greater than 90 days following end of previous prescription.

et al.[10] Genetic associations between specific human leucocyte antigen molecules and GCA have been found,[26] although none yet for PMR.[27] However, as no major variation has been found in the genetic make-up of people between different regions around the UK, it is unlikely to be the reason for this difference.[28] Other potential reasons include an association between social class and PMR, a viral aetiological agent, or environmental differences such as reduced vitamin D levels in the north of the UK due to less sunlight exposure, which may lead to vitamin D deficiency being diagnosed preferentially.

Smeeth *et al*[10] found that the incidence of PMR in the UK was increasing until 2001, which we replicated. However following this date, the incidence rate plateaued.

With regard to GC therapy, 75% received a first dose between 8 and 21 mg, which corresponds well to the recommended starting dose of 12.5–25 mg.[2] The median duration of treatment of patients with GC in our sample is, however, less than that found by Shbeeb *et al*[29] in their recent study into GC prescribing in a cohort of 359 patients with PMR in Olmsted County, Minnesota. The median dose prescribed was similar, at around 5 mg, but the length of treatment was greater, with only 19% of patients discontinuing therapy in the first year of treatment, compared with 27% in our data. A number of reasons for this difference could be suggested; for example, their patients may represent more severe variants of the condition; they defined end of treatment as permanent discontinuation of GC therapy rather than a gap of 90 days or 6 months; and their inclusion criteria were stricter. Therefore some of the patients included in our study may have gone on to be reclassified with a different condition and have GC therapy curtailed earlier. Our sensitivity analyses of patients who had a record of referral to secondary care rheumatology services confirmed this group had longer continuous and total treatment. Both studies agreed though that a significant proportion of patients were subject to prolonged treatment with GCs.

Previous studies have shown that long-term GC treatment increases a person's risk of a wide range of medical conditions.[22] This is the first study of a large population which confirms the existence of a prolonged 'symptom tail' in PMR, wherein a significant number of patients receive a higher average daily dose, a larger total dose, more individual prescriptions of GC and receive their treatment over a longer period of time.

The reason behind this symptom tail could be a more severe subtype of PMR or a different underlying diagnosis, for example rheumatoid arthritis, for which referral for secondary care review may be appropriate. Alternatively, it may represent GCs masking the symptoms of other comorbidities which flare on reduction of GC treatment or adrenal insufficiency following prolonged GC use.

CONCLUSION AND CLINICAL IMPLICATIONS

In conclusion, we have established the burden that PMR places on the UK health service. Due to the ageing population, the prevalence of PMR in the UK is increasing, although the incidence rates appear to have stabilised. Analysis of high-quality, routinely collected primary care data has enabled us to confirm that a significant proportion of patients with PMR receive prolonged treatment with GC, contrary to previously held norms that cure will be achieved within 2 years. Long-term GC therapy is associated with a number of serious adverse effects,[22] which is both dose-dependent[30] and duration-dependent[31]. Early identification of patients who are likely to be subject to prolonged GC therapy is a priority area for future research. These patients could then be prioritised for referral to secondary care for consideration of GC-sparing agents.

Contributors Study design: RJP, SM, TH, CDM, AAS. Literature search: RJP. Data management: AAS. Data analysis, data interpretation: RJP, AAS. First draft and figures: RJP. Critical revision of drafts: SM, TH, CDM, AAS.

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Disclaimer This study is based in part on data from the Clinical Practice Research Datalink GOLD database obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the author(s) alone.

Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by CPRD's inhouse Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number: 17_203RA).

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APPENDIX 4: Systematic review paper

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Comorbidities in polymyalgia rheumatica: a systematic review

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Abstract

Background and aim: Comorbidities are known to exist in many rheumatological conditions. Polymyalgia rheumatica (PMR) is a common inflammatory rheumatological condition affecting older people which, prior to effective treatment, causes severe disability. Our understanding of associated comorbidities in PMR is based only on case reports or series and small cohort studies. The objective of this study is to review systematically the existing literature on the comorbidities associated with PMR.

Methods: MEDLINE, EMBASE, PsycINFO and CINAHL databases were searched for original observational research from inception to November 2016. Papers containing the words 'Polymyalgia Rheumatica' OR 'Giant Cell Arteritis' OR the terms 'PMR' OR 'GCA' were included. Article titles were reviewed based on pre-defined criteria by two reviewers. Following selection for inclusion, studies were quality assessed using the Newcastle–Ottawa tool and data were extracted.

Results: A total of 17,329 papers were reviewed and 41 were incorporated in this review, including three published after the search took place. Wide variations were found in study design, comorbidities reported and populations studied. Positive associations were found between PMR diagnosis and stroke, cardiovascular disease, peripheral arterial disease, diverticular disease and hypothyroidism. Two studies reported a positive association between PMR and overall malignancy rate. Seven studies reported an association between PMR and specific types of cancer, such as leukaemia, lymphoma, myeloproliferative disease and specified solid tumours, although nine studies found either no or negative association between cancer and PMR.

Conclusion: Quantification of the prevalence of comorbidities in PMR is important to accurately plan service provision and enable identification of cases of PMR which may be more difficult to treat. This review highlights that research into comorbidities in PMR is, overall, methodologically inadequate and does not comprehensively cover all comorbidities. Future studies should consider a range of comorbidities in patients with a validated diagnosis of PMR in representative populations.

Keywords: Polymyalgia rheumatica, Giant cell arteritis, Systematic review, Comorbidities, Multimorbidity, Epidemiology

Introduction

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatological condition affecting people over the age of 50 years [1]. Symptoms include muscle stiffness and pain, predominantly around the neck or shoulder and pelvic girdles [2], as well as a low-grade fever, depression, fatigue, anorexia and weight loss [3, 4]. Raised inflammatory markers (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)) are a hallmark of this condition. PMR is usually treated with medium/low dose oral glucocorticoids (GCs) which are gradually reduced and stopped over several years [5].

Patients with common inflammatory rheumatological conditions, for example gout [6] and rheumatoid arthritis (RA) [7], are predisposed to developing cardiovascular disease (CVD). In patients with RA, this risk has been attributed to an increased prevalence of arterial atherosclerotic plaques [8, 9], the quantity of which are correlated with levels of systemic inflammation [10] and duration of

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rheumatological disease [11]. Patients with RA are also known to have a higher risk of lung diseases [12] and certain types of cancers, particularly haematological cancers [13]. PMR, like RA, is a rheumatological condition characterised by increased levels of inflammation, and therefore patients with PMR may have a similar predisposition to increased risks of certain conditions.

In order to diagnose PMR, guidelines endorsed by the American College of Rheumatology and the European League Against Rheumatism advise the exclusion of conditions which may cause similar symptoms [14]. These include core exclusion conditions (GCA, cancer and infections) as well as RA, fibromyalgia, hypothyroidism and drug-induced myalgia. The guidelines also suggest an evaluation of whether patients have comorbidities that put them at greater risk of side effects from GC treatment [14]. Quantifying the burden of comorbidities in this group of patients is therefore important.

The age group (typically over 50 years) most commonly affected by PMR frequently has more than one comorbidity. Aging is an important predictor of multimorbidity; a recent Scottish study found the number of adults with two or more chronic conditions increased from 30.4% between age 45 and 64 years, to 64.9% in those aged 65–84 years, to greater than 80% in those aged over 85 years [15]. This systematic review aims to summarise the available evidence of the comorbidity profile of people with PMR, and will be the first review to assess comprehensively the evidence for all comorbidities and whether there is evidence for multiple comorbidities existing together. If the evidence shows that patients with PMR commonly have multiple comorbidities then these may no longer be viewed as exclusion criteria precluding a diagnosis of PMR, potentially revealing the true burden of PMR to be higher than currently recognised.

Methods

We conducted a systematic review and narrative synthesis of research literature. We searched medical bibliographic databases to identify articles containing data on any comorbidity either preceding or following a diagnosis of PMR.

Data sources, searches and study selection

The search was conducted in MEDLINE, EMBASE, PsyciINFO and CINAHL from their inception until the date of search in November 2016. Additional articles were found by examining reference lists of included studies and an updated search was run in June 2018 which led to the inclusion of a further study. The exploded MeSH terms 'polymyalgia rheumatica' and 'giant cell arteritis' were used in combination with text word searches for the same as well as for 'PMR' and 'Giant Cell Arteritis' (GCA). GCA is a vasculitis which very commonly co-occurs with PMR; around 10–30% of patients with PMR develop GCA during the course of their illness [16, 17]. Given this overlap in conditions, GCA was included to increase the likelihood of ensuring that all studies in which PMR comorbidities were considered were included in the review. PRISMA guidelines were followed throughout the review process [18].

All article titles identified were screened by a single reviewer (RP) against the inclusion and exclusion criteria. A random sample of 100 of these titles was reviewed by a second reviewer (TH) and agreement between decisions was assessed using adjusted κ calculation [19]. All selected abstracts were then assessed by two reviewers (RP and TH). Any citation thought to be eligible by either reviewer was carried forward to full text review. Reasons for exclusion were recorded. Finally, the remaining full texts were reviewed by the same two authors and a list of papers to be included in the narrative synthesis was created.

Inclusion and exclusion criteria

The inclusion criteria for this review included: a sample of patients with PMR and at least one comorbidity; and the study design must be either cross-sectional, case–control or a prospective or retrospective cohort study. Exclusion criteria were: patients under the age of 40 years; randomised control trials (RCTs); and review articles or conference abstracts. PMR is a disease of older adults. In order to make a diagnosis of PMR, clinical guidelines suggest patients must be aged over 50 years [20], therefore patients under 40 years old are likely to represent misdiagnosis. RCTs were excluded as we wished to look at representative samples of patients with PMR drawn from real-world, observational data. Review articles and conference abstracts were not included to ensure all articles were peer reviewed and fully referenced. In order to ensure that all conditions represented true comorbidities, rather than secondary complications of GC treatment in PMR, we excluded trials which reported only complications of GC therapy [3, 21–27].

There were no date or language restrictions although all included studies were in English. Potentially relevant studies that contained data on GCA were included until full text review due to the overlap between PMR and GCA. If, at that point, the paper only contained data about GCA, it was excluded. The reference lists of other systematic reviews that had assessed individual comorbidities related to PMR were also reviewed to reduce the chance of missing relevant studies.

Quality assessment

Both reviewers, using the Newcastle–Ottawa Scale for case–control and/or cohort studies [28], evaluated the quality of studies. This scale was chosen as it is endorsed for use in systematic reviews of non-randomised trials by the Cochrane Collaboration [29].

Data extraction

A standardised form was developed and used by both reviewers independently to ensure the accuracy of data extraction (Additional file 1). The primary outcome of interest was the total number of patients with PMR who developed a comorbidity of interest compared to controls (without PMR). Other data extracted included clinical criteria used to diagnose PMR, study design, comorbidity under investigation and its temporal relationship to PMR. Meta-data from each study, such as lead author name, publication year, sex, age, country and healthcare setting, were also extracted. Comorbidities were categorised into four groups: malignant disease, particularly haematological malignancies; vascular disease, including coronary, cerebroarterial and peripheral arterial disease; mortality; and other comorbidities (e.g. endocrine, psychiatric and neurological diseases).

Data analysis

Using the total number of patients with PMR and, if present, their controls we attempted to aggregate data to obtain pooled estimates of prevalence of comorbidities and odds ratios to quantify the strength of any apparent association.

Results

Search results

A total of 27,698 articles were identified in this search with a further seven identified following review of references of other articles. Of this total, 10,376 were removed due to duplications, leaving 17,329 unique articles. Following application of inclusion and exclusion criteria during screening of titles, 17,042 further citations were excluded. Of the random selection of 100 of these articles which were reviewed by a second author, agreement between authors was excellent ($\kappa = 0.86$).

The abstracts of 287 studies were assessed for eligibility, and 131 were excluded at this stage. The full texts of articles were reviewed and 41 were retained for data extraction [30–70]. This process, which followed PRISMA guidelines, including reasons for exclusion of studies [18], is illustrated in Fig. 1.

Articles included in the review

Of the 41 included studies, 32 were cohort studies [30–61] and nine were case–control studies [62–70]. Eighteen of the cohort studies did not use a formal comparator group. Of the 14 cohort studies with controls, six were based on national datasets, whereas eight were based either on local datasets or on patients presenting to clinics at the same hospital. PMR cases were defined from medical records in 16 studies, national registries in 19 studies and national databases in the remaining six studies. Co-existent GCA cases were formally excluded in six studies and included, or not explicitly excluded, in 35 studies. All but one study was from Europe (predominantly Scandinavia) or the United States. Included studies are tabulated in Additional file 2.

PMR and cancer

Seven studies, reporting 12 outcome measures, have assessed the risk of cancer diagnosis prior to PMR onset (Table 1). All of these studies excluded PMR diagnoses made in the year prior to diagnosis of cancer, to reduce the risk of reverse causality (i.e. cancer causing PMR or PMR symptoms). Of these, the rate of haematogenous cancers was significantly higher among patients with PMR in five cases, while the other seven were non-significantly different.

Six studies reported prospective rates of any cancer diagnosis after diagnosis with PMR (Table 2); two showed an increase in the proportion of people with PMR who developed cancer compared to controls, two were equivocal and the remaining two found the opposite.

In six prospective cohort studies the risk of 17 types of cancer following diagnosis with PMR was considered. Two studies showed an increase in the risk of Hodgkin's lymphoma [55] and non-Hodgkin's lymphoma [56]. Of the remaining four studies, three reported no difference in the rates of female cancers [51], upper gastrointestinal cancers [47] or myeloma [54]. The final study reported no difference in mortality following diagnosis with gastrointestinal cancers [50] among people with or without PMR.

PMR and vascular disease

A number of studies ($n = 8$) have assessed a variety of different vascular diseases in patients with PMR (Table 3). Fifteen outcome measures were reported, although only seven gave comparable figures for patients without PMR. In each study with a comparator group the proportion of people with PMR who developed vascular disease was higher compared to controls.

PMR and mortality

Few studies have assessed the association between PMR and mortality ($n = 4$). Three studies reported reduced mortality among patients diagnosed with PMR [35, 38, 39] while one study found an increase, but this study did not differentiate between patients with PMR and GCA [36].

PMR and other comorbidities

An association between thyroid disease and PMR is unproven. Bowness et al. [31] found an increase in the risk of hypothyroid disease (RR 3.2 (95% confidence interval 1.71, 5.91)), but Juchet et al. [33] did not. One recent case–control study found a significantly increased rate of diverticular disease prior to a diagnosis with PMR (OR 4.06 (95% CI 1.76–9.35)) [70].

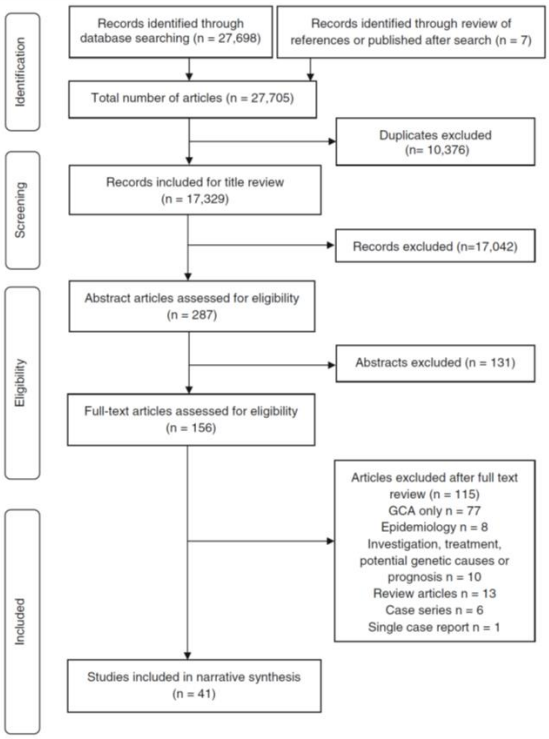

Fig. 1 Flowchart of study inclusion, adopted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. GCA giant cell arteritis

No evidence has been found to associate PMR with psychiatric comorbidities, including schizophrenia [44, 69] and bipolar disease [44]. Li et al. [49] found a potential association between PMR and Parkinson's disease (SIR 1.25 (95% CI 1.01, 1.53)). Hemminki et al. [53] also reported an association between PMR and hospitalisation due to obesity (SIR 1.65 (95% CI 1.22, 2.19)).

A small number of studies from the United States (n = 2) [40, 59] looked at wide ranges of different comorbidities but their sample size was insufficient to find significant associations for the majority of the comorbidities.

Quality assessment

All of the articles in this study used medical records or nationwide registries (based on medical records) to corroborate diagnosis of PMR and the comorbidity; therefore, they were awarded three or four stars for cohort or case selection using the Newcastle–Ottawa criteria. All studies also achieved at least two stars for outcome measurement. However, many of the studies failed to recruit a comparator group, instead using the population as a reference, and therefore comparability scores were low (Additional file 2).

Many of the cohort studies identified failed to include comparison groups (n = 18), instead using indirect standardisation to calculate incidence or mortality ratios. The lack of comparison groups limits the generalisability of many of the studies. Further to this, almost half of the studies (n = 19) sourced their sample of patients with PMR based on hospital discharge data. This may be an appropriate approach for some autoimmune conditions, but the majority of patients with PMR are managed in primary care settings [71, 72].

Aggregation of data to calculate pooled odds and hazard ratios was attempted for vascular disease and cancer diagnoses; however, high levels of heterogeneity were

Table 1 Cancer prior to diagnosis with PMR

Retrospective case–control study								
Study	Diagnosis	Cases (*n*)	PMR cases (*n*)	Controls (*n*)	PMR controls (*n*)	Odds ratio (95% CI)	Case rate (%)	Control rate (%)
Anderson et al. [64]	Lymphoid malignancies	33,721	344	122,531	1244	0.9 (0.8–1.0)	1.02	1.02
Anderson et al. [63]	Myeloid malignancy	9998	125	160,086	1288	1.7 (1.4–2.1)	1.25	0.80
	Myelodysplastic malignancy	3758	55	42,886	518	1.5 (1.1–2)	1.46	1.21
Anderson et al. [67]	HCL	418	9	160,086	2721	1.5 (0.5–3.9)	2.15	1.70
Askling et al. [62]	All lymphoma	42,676	114	78,487	250	0.8 (0.7–1.0)	0.27	0.32
	NHL	28,355	88	52,164	187	0.9 (0.7–1.1)	0.31	0.36
	HL	4037	3	7394	15	0.4 (0.1–1.3)	0.07	0.2
	CLL	10,555	24	19,391	52	0.8 (0.5–1.4)	0.23	0.27
Kristinsson et al. [66]	Any MPN	11,039	46	43,550	104	1.7 (1.2–2.5)	0.42	0.24
Lanoy and Engels [65]	Cutaneous NHL	2652	19	178,452	1731	0.7 (0.5–1.1)	0.72	0.97
Lindqvist et al. [68]	MM	19,112	56	75,408	116	1.9 (1.4–2.6)	0.29	0.15
	MGUS	5403	58	21,209	79	2.9 (2.1–4.1)	1.07	0.37

PMR polymyalgia rheumatica, *HCL* hairy cell leukaemia, *NHL* non-Hodgkin's lymphoma, *HL* Hodgkin's lymphoma, *CLL* chronic lymphocytic leukaemia, *MM* multiple myeloma, *MPN* myeloproliferative neoplasm, *MGUS* monoclonal gammopathy of undetermined significance

found between the studies (88–100%) and therefore this was not reported.

Many of the studies limited themselves to a small number of comorbid conditions, thus not allowing a picture of the overall health of patients with PMR to develop. Two studies [34, 40] did attempt to look at a range of comorbidities but they were underpowered.

Discussion

Statement of principle findings

This review found some evidence of an association between PMR and vascular disease, and possibly cancer, particularly in the first 6 months following diagnosis. However, the evidence for this is not robust.

Table 2 Cancer following diagnosis with PMR

Prospective cohort with combined cancer cases						
	PMR patients			Control patients		
Study	PMR cases (*n*)	Cancer cases (*n*)	Proportion (%)	Controls (*n*)	Cancer cases (*n*)	Proportion (%)
Muller et al. [57]	2877	667	23.18	9942	1938	19.49
Bellan et al. [61]	100	24	24.00	702	41	5.84
Ji et al. [45]	35,918	3941	10.97	–	–	–
Myklebust et al. [37]	366	34	9.29	1324	143	10.80
Haga et al. [32]	91	10	10.99	794	131	16.50
Pfeifer et al. [59]	359	66	18.38	357	62	17.37
Total[a]	39,711	4742	21.12	13,119	2315	17.65

PMR polymyalgia rheumatica
[a]Ji et al. [45] not included in calculation as no control group

The concentration of the apparent association between PMR and cancer in the first 6 months following diagnosis suggests the possibility of an element of misdiagnosis. This could occur as some of the features of PMR (myalgia, fatigue, weight loss, raised inflammatory markers) are also non-specific early features of some cancers. Furthermore, as time passed, the rate of diagnosis of cancer was found to drop down to the background population rate.

Regarding specific types of cancer, some studies have proposed there could be associations between PMR and haematological cancers. This includes Hodgkin's and non-Hodgkin's lymphoma [56], myeloma [68] and other myeloid malignancies [63, 66]. An increase in the risk of lymphoma has been observed with RA, which has been postulated to be due to higher accumulated inflammatory activity in RA [73]; a similar mechanism may lie behind the apparent increase in patients with PMR.

The overall trend of results suggests that PMR may be associated with an increased risk of the development of vascular disease. Knowing that both PMR and RA are inflammatory conditions, there is biological plausibility that PMR and vascular disease could be associated. However, the two largest studies, both based on population data from the UK, reported conflicting results: Hancock et al. [58] stated that PMR was significantly associated with vascular disease, while Pujades-Rodriguez et al. [60] reported a reduction in the risk (incidence rate ratio 0.88 (95% CI 0.83–, 0.94)). However, in the latter study when only patients with PMR were included, there was a slight increase in the proportion of patients with the condition who went

on to have a vascular event compared to controls (23.24% compared to 20.43%).

These two studies employed similar approaches selecting with PMR from linked UK databases. However, a number of differences existed between the studies, including the age of participants (> 50 years only for Hancock et al. [58] and > 18 years for Pujades-Rodriguez et al. [60]), average years of follow up (7.8 and 3.13 years respectively) as well as the total number of patients found with PMR (3249 compared to 11,320 patients). Potentially, the variation in risk of vascular events between these studies could be explained by the differences in follow up or the age distribution of the study population.

Another reason for inconsistent evidence of an increase in vascular risk for patients with PMR may be the modulating effect that GCs have upon levels on inflammation. If the risk of vascular disease correlates with the presence of inflammation in the body, GC therapy would reduce this, which may then also reduce vascular risk. The study by Kremers et al. [42] appears to bear this out. In this study, the risk of vascular events was lower in patients with PMR who were treated with GCs compared to those who were not. Further to this, Hancock et al. [58] reported that the excess vascular risk in PMR reduced over time; this could reflect declining levels of inflammation.

Overall, although some studies dissent from this view, it appears that a diagnosis of PMR increases an individual's risk of vascular disease. However, further research in this area is needed to add clarity.

Conversely, it appears that a diagnosis with PMR is associated with a reduction in mortality. This was demonstrated in three out of the four studies that reported it as an independent outcome. A possible explanation for this could again be surveillance bias. Patients with chronic illness (and especially PMR where regular assessment, follow up and monitoring are advised) are more likely to be under active follow up for their condition and any developing morbidity, particularly if related to well-recognised adverse effects of treatment, is likely to be identified and managed earlier.

There is a small amount of evidence that patients with PMR may be more likely to develop hypothyroidism [31] and Parkinson's disease [49]. PMR and hypothyroidism both preferentially affect females, and therefore a similar autoimmune pathway may be present in both conditions. However, as has been pointed out, PMR does not share all of the characteristics of traditional autoimmune conditions, for example it lacks specific autoantibodies [74].

Table 3 Vascular disease and PMR

Study	PMR patients			Control patients		
	PMR cases (*n*)	Comorbid condition (*n*)	Proportion (%)	Controls (*n*)	Comorbid condition (*n*)	Proportion (%)
Stroke						
Kang et al. [46]	781	113	14.47	3905	273	6.99
Zoller et al. [48]	16,496	1981	12.01			
Kremers et al. [42]	276	58	21.01			
Hancock et al. [58]	3249	397	12.22	12,735	556	4.37
Myocardial infarction						
Kremers et al. [42]	276	47	17.03			
Hancock et al. [58]	3249	460	14.16	12,735	575	4.52
Zoller et al. [48]	21,351	5669	26.55			
Heart failure						
Kremers et al. [42]	276	68	24.64			
Peripheral vascular disease						
Kremers et al. [42]	276	35	12.68			
Hancock et al. [58]	3249	140	4.31	12,735	151	1.19
Warrington et al. [43]	353	38	10.76	705	28	3.97
Combined						
Kremers et al. [42]	276	208	75.36			
Hancock et al. [58]	3249	918	28.25	12,735	1150	9.03
Pujades-Rodriguez et al. [60]	9776	2272	23.24	105,504	21,559	20.43
Bengtsson and Malmvall [30]	73	16	21.92			

PMR polymyalgia rheumatica

Furthermore, it seems that PMR is not associated as strongly with other autoimmune conditions as would be expected if it was a pure autoimmune disease. Parkinson's disease is a condition which predominantly affects older people, as does PMR, and therefore this association may just be a result of clustering of diagnoses in an older population.

Strengths and weaknesses

The main strength of the study was its deliberately broad scope and aim to include any study in which the risk of any comorbidity either before or after diagnosis with PMR was to be reviewed. Following the initial broad search, articles from the 'grey literature' were excluded and only articles fully published in peer-reviewed journals were included.

The potential limitations in this study arose not due to the protocol but rather because the majority of studies were of relatively poor quality. These risks included selection bias, surveillance bias and a lack of adequate control groups.

Selection bias within the included studies is a possibility in this review, as the majority of studies drew PMR cases from secondary care, either from hospital discharge data or from rheumatology outpatient clinics. Current UK guidelines suggest only referring atypical cases, cases of diagnostic uncertainty or treatment predicaments [5, 14], meaning that in the UK 71–84% of patients with PMR are treated in the community by primary care physicians [71, 72]. Therefore, the patient population in these studies may not accurately reflect the majority of those who are diagnosed with PMR. This may have artificially inflated the apparent differences in development of comorbidities between patients with and without PMR.

Another limitation is the risk of surveillance bias as discussed earlier around the apparent reduction in mortality [75]. Some case–control studies attempted to deal with this by excluding comorbid disease found in the year prior to diagnosis [63, 64, 67, 68], while in two observational cohort studies [58, 60], controls were selected that had contacted a primary care service in the year the index cases were diagnosed. Finally, many of these studies assessed multiple variables, often > 30 different autoimmune conditions, increasing the likelihood of a chance finding (type II error).

Furthermore, we also noted that the range of comorbidities reported in the literature was more limited than we expected; for example, there were no studies which explicitly examined the risks of important and common conditions such as diabetes mellitus and asthma or other chronic respiratory conditions.

A further potential bias is the effect of GC therapy and the impact of this on the risks of comorbidities. As GC is the only widely accepted treatment for PMR, we could not exclude studies where patients were treated with GC. To reduce the impact of potential bias from GC treatment, we excluded studies in which direct complications of GC therapy were assessed. However, as discussed previously in relation to vascular risk, GC therapy is inevitable in PMR and therefore we could not completely mitigate this effect.

Conclusion

This review has found the overall standard of evidence regarding the association of comorbidities with PMR to be weak. There may be an increased risk of vascular disease and possibly cancer in patients with PMR. Weaker quality evidence also suggests that patients with PMR have a reduced mortality rate. Currently, there is little evidence around the wider health of patients with PMR either at the time of diagnosis or in the period following.

This lack of firm evidence around which comorbidities exist alongside or are potentially associated with PMR presents a problem for the pragmatic clinician. Current clinical guidelines suggest that in order to diagnose PMR, a large number of other conditions which may mimic the symptoms of PMR should be excluded. This list includes, but is not limited to, rheumatoid arthritis and endocrine, infective and neoplastic conditions [14]. However, comorbidities are very common in the age group affected by PMR [76], and therefore the coexistence of one of these comorbidities with PMR should not necessarily prevent or invalidate the diagnosis of PMR.

The uncertainty around the general health of patients with PMR and comorbidities that may coexist with it presents a challenge for healthcare practitioners who deal most with this condition, be they from primary or secondary care. A rigorous diagnostic and follow-up process is crucial to ensure this uncertainty does not translate into misdiagnosis. In the future, it is important to confirm whether, and if so to what extent, a diagnosis of PMR imparts an excess risk of vascular disease or cancer.

Further research in the form of large observational studies, based in primary care, of the health of patients with PMR, including the prevalence of comorbidities before and after diagnosis, would allow clinicians to better monitor for these outcomes.

Additional files

Additional file 1: Data collection form (DOCX 18 kb)
Additional file 2: Details of all included studies (DOCX 72 kb)

Abbreviations

CRP: C-reactive protein; CVD: Cardiovascular disease; ESR: Erythrocyte sedimentation rate; GC: Glucocorticoid; GCA: Giant cell arteritis;

PMR: Polymyalgia rheumatica; RA: Rheumatoid arthritis; RCT: Randomised control trial

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Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Authors' contributions
RP, TH, SM, CM and AAS contributed to study design. RP performed the literature search, RP and TH the title, abstract and full text review. RP produced the first draft of the manuscript and the tables. SM, TH, CM and AS performed critical revision of the manuscript drafts. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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APPENDIX 5: Data collection form for systematic review

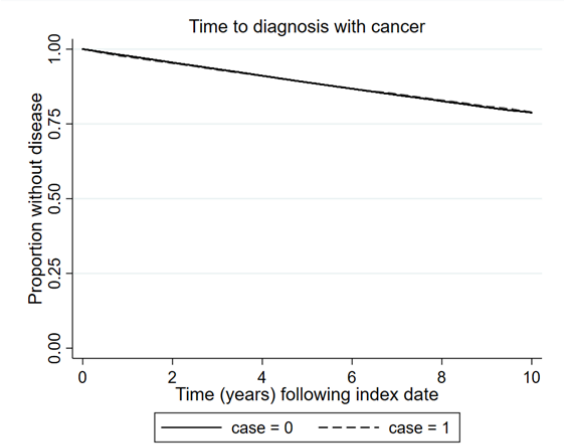
Study ID		
Author		
Title		
Journal		
Year		
Volume		
Issue		
Page numbers		
Language of publication		
Continent where data collection occurred		
Sample size	PMR:	Controls:
Average Age	PMR:	Controls:
Sex distribution	PMR:	Controls:

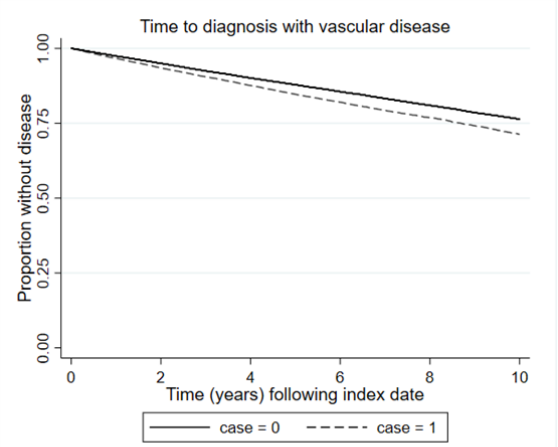
PMR Clinical Criteria Used		**Study design**	
Chuang		Cohort	
Bird		Case control	
Jones		Cross sectional	
Nobunaga		Population	
Healey		Systematic Review	
Hunder			
EULAR-ACR			
Not referenced			

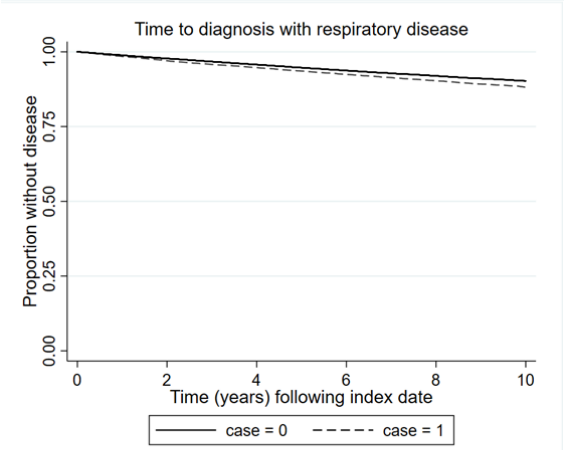
Name of comorbidity(s)	**Retrospective**	**Prospective**

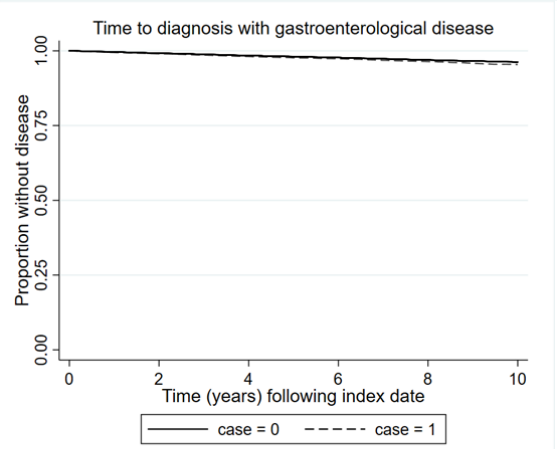
	N		N
Cases		Controls	
Comorbid condition		Comorbid condition	
Proportion affected / Case rate		Proportion affected / Case rate	
Person years follow up		Person years follow up	
Incidence rate / Odds		Incidence rate / Odds	
Incidence rate or Odds ratio			
Effect Measures from paper			

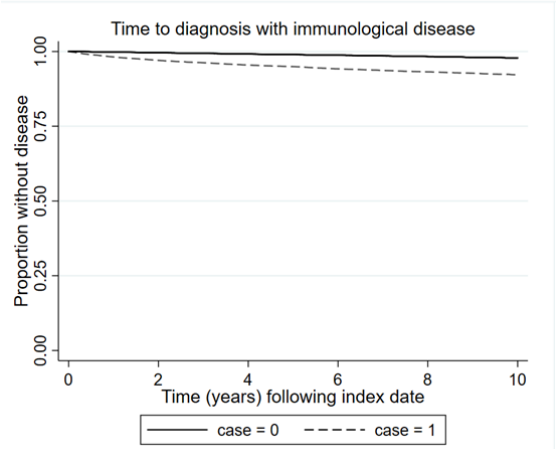
APPENDIX 6: Kaplan Meier estimates of time to development of comorbidities

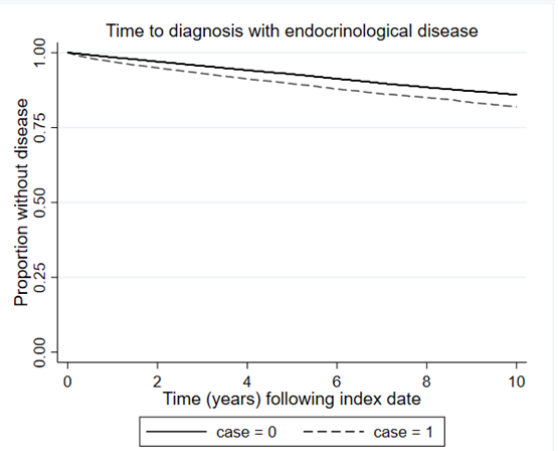


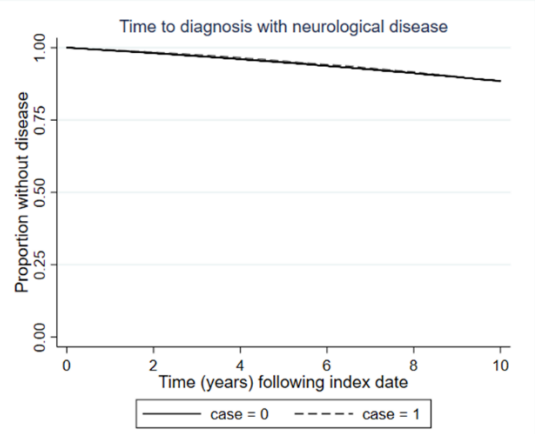


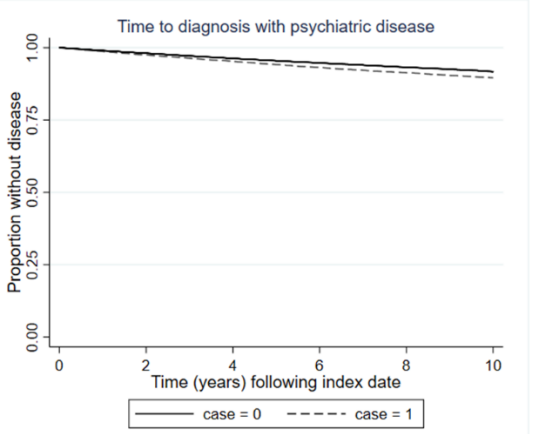


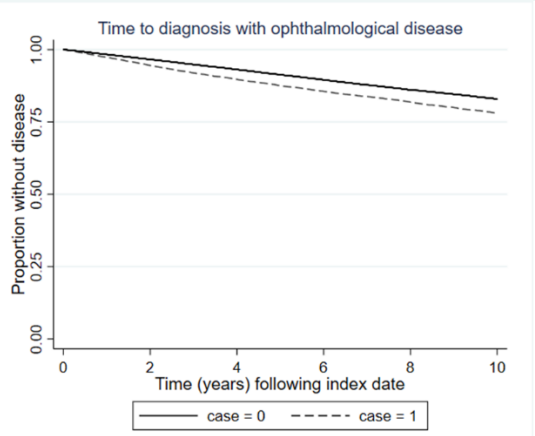


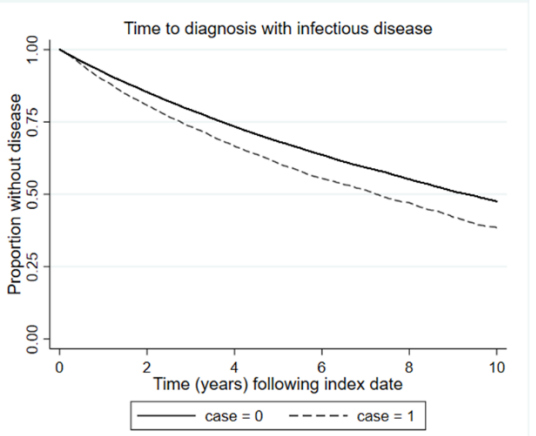


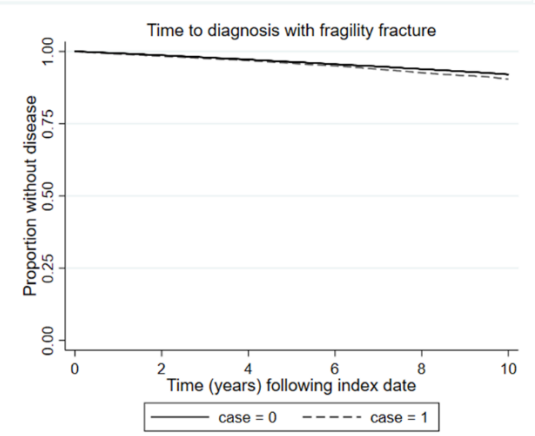


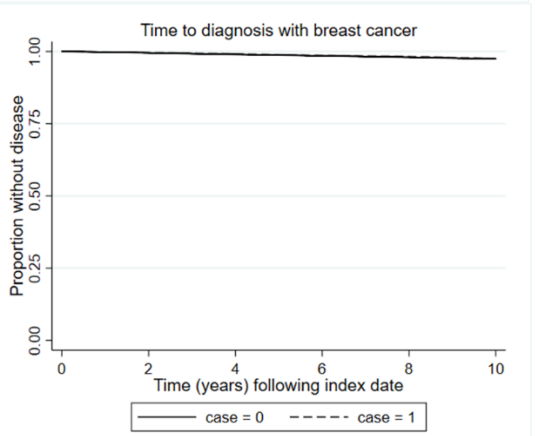

Time to diagnosis with neurological disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

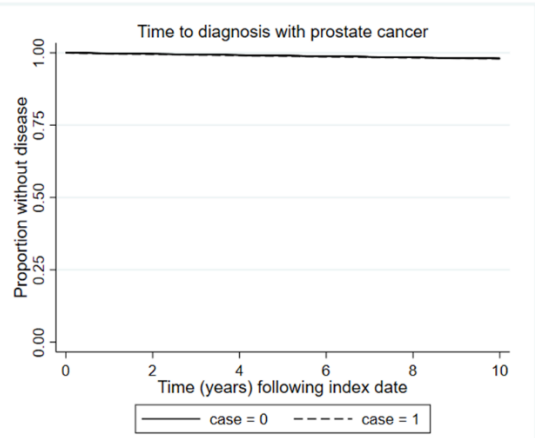

Time to diagnosis with psychiatric disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

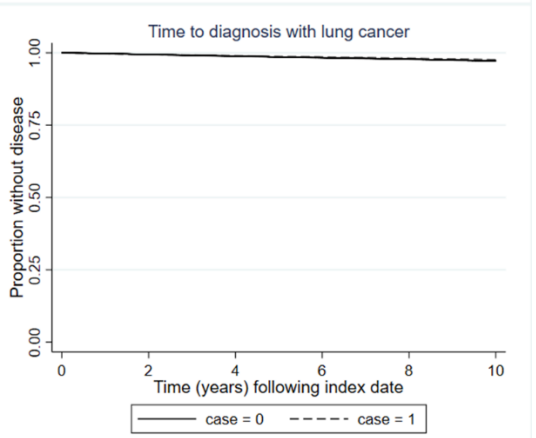

Time to diagnosis with ophthalmological disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

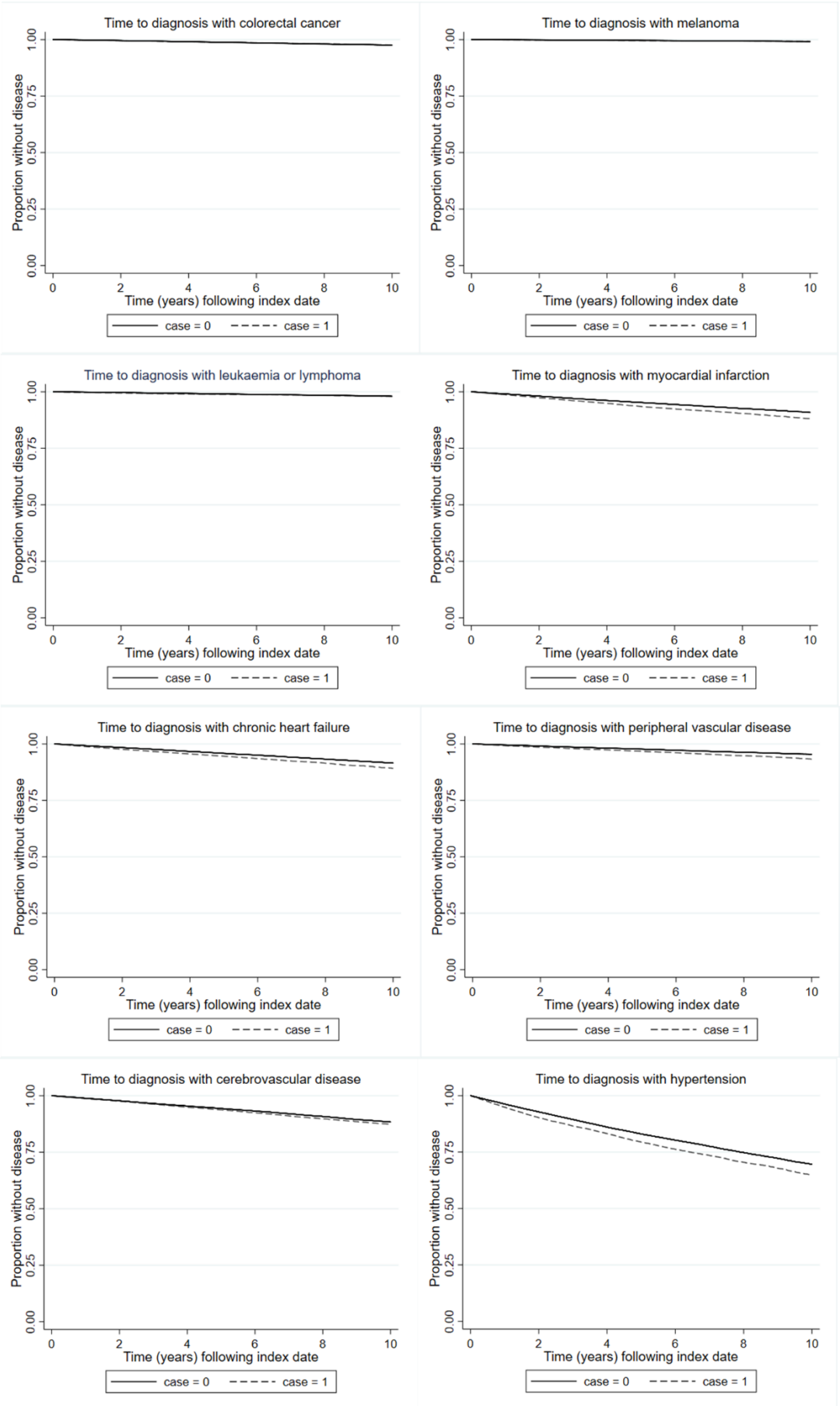

Time to diagnosis with infectious disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

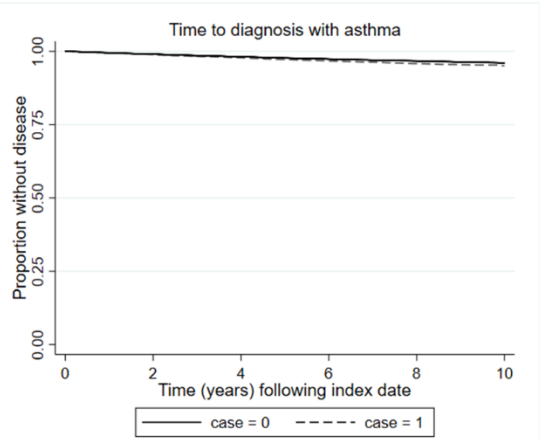

Time to diagnosis with fragility fracture
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

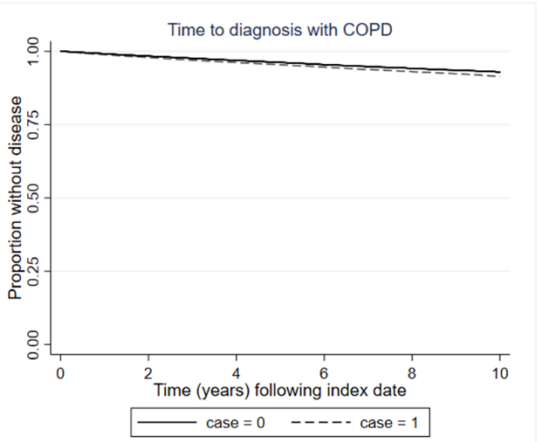

Time to diagnosis with breast cancer
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

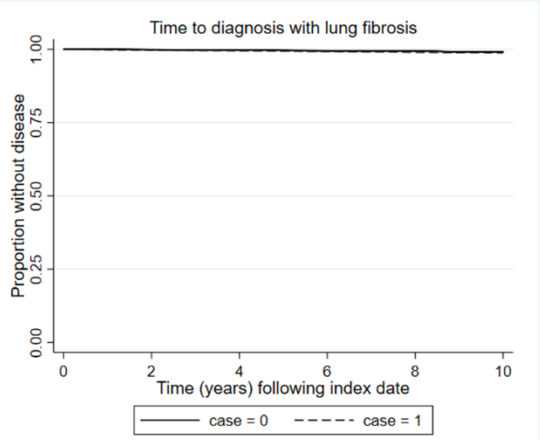

Time to diagnosis with prostate cancer
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

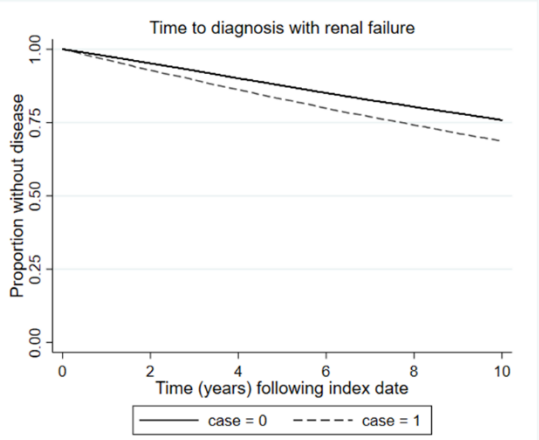

Time to diagnosis with lung cancer
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

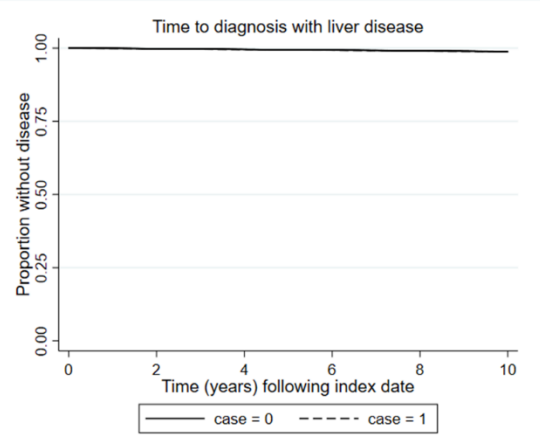

Time to diagnosis with colorectal cancer
Time to diagnosis with melanoma
Time to diagnosis with leukaemia or lymphoma
Time to diagnosis with myocardial infarction
Time to diagnosis with chronic heart failure
Time to diagnosis with peripheral vascular disease
Time to diagnosis with cerebrovascular disease
Time to diagnosis with hypertension
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

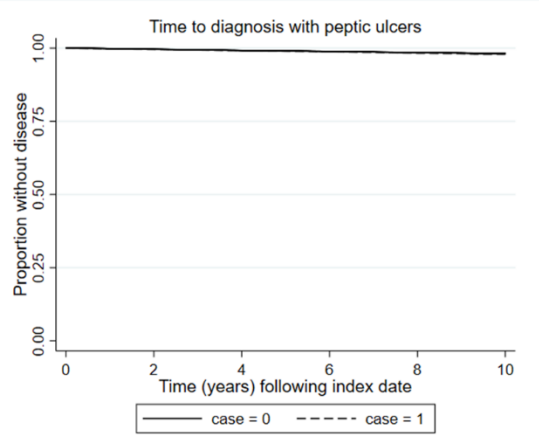

Time to diagnosis with asthma
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

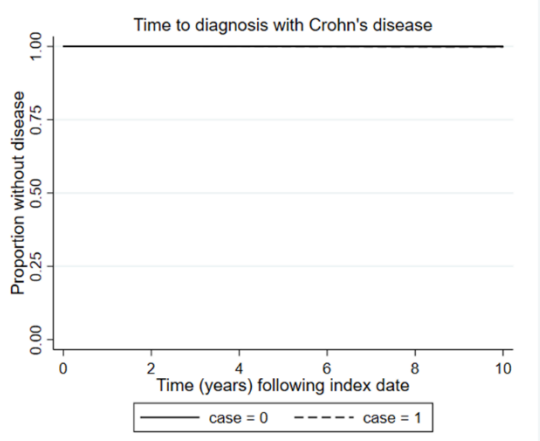

Time to diagnosis with COPD
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

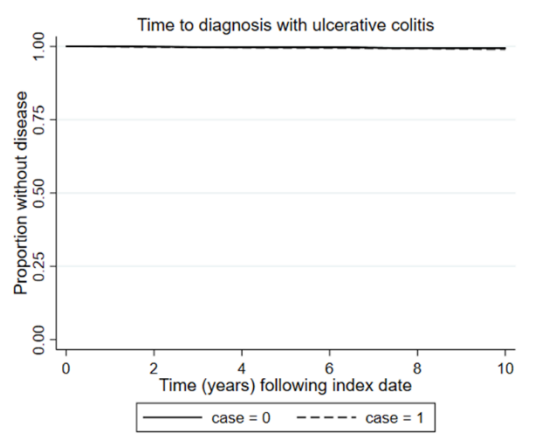

Time to diagnosis with lung fibrosis
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

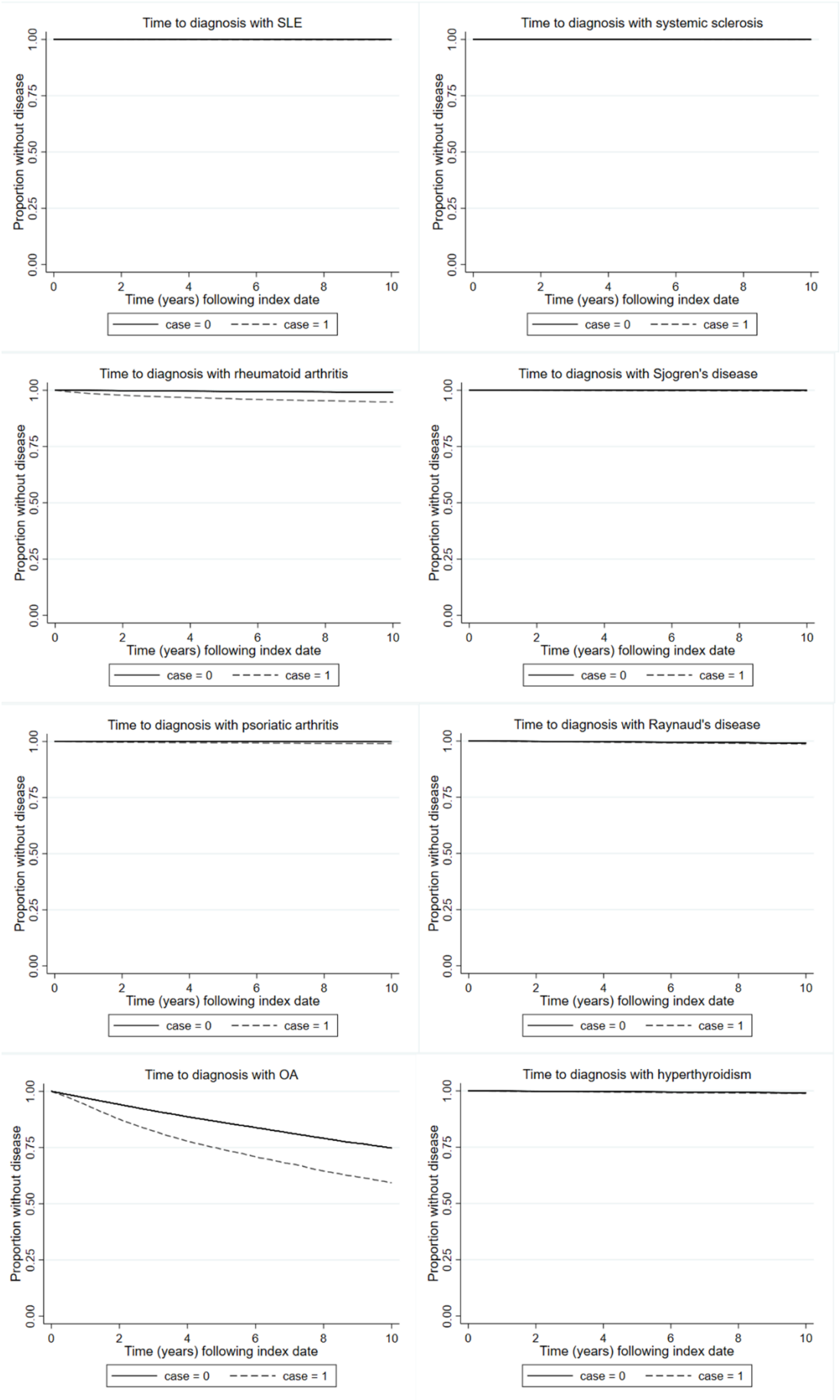

Time to diagnosis with renal failure
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

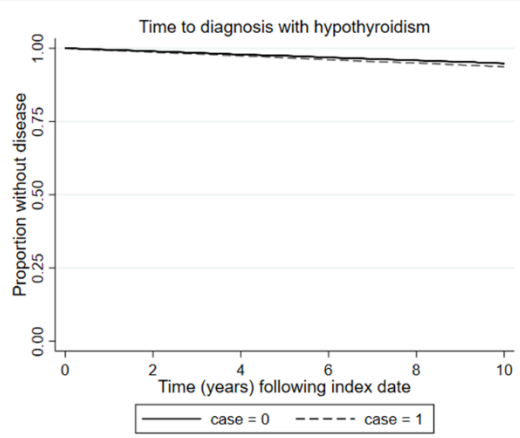

Time to diagnosis with liver disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

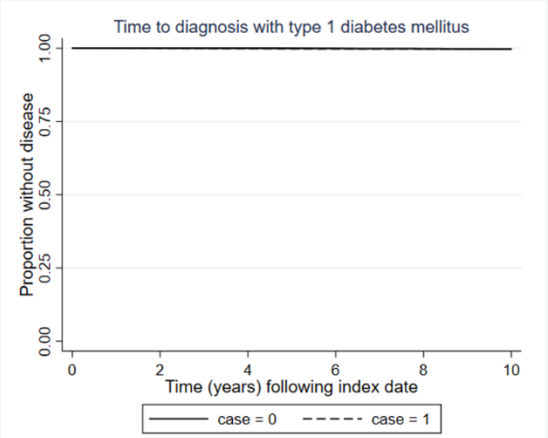

Time to diagnosis with peptic ulcers
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

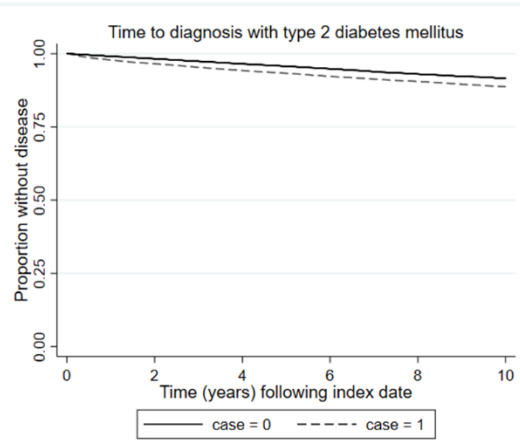

Time to diagnosis with Crohn's disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

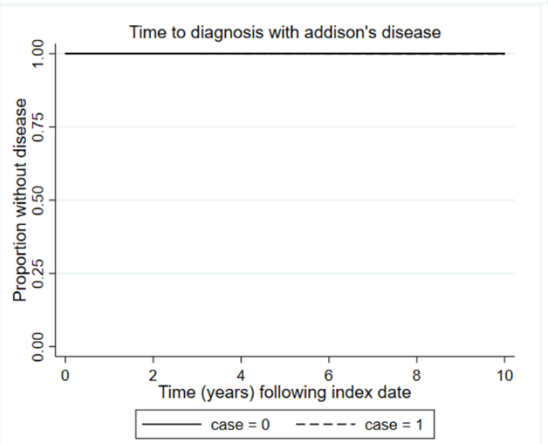

Time to diagnosis with ulcerative colitis
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

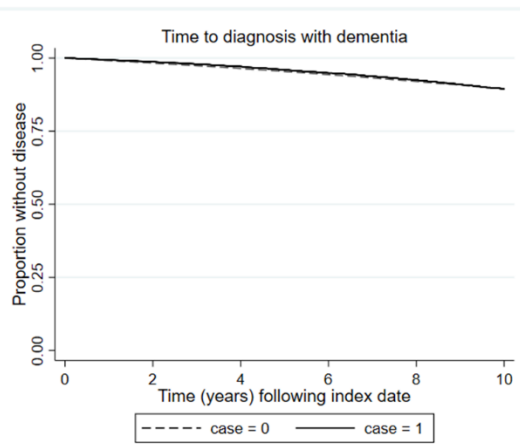

Time to diagnosis with SLE
Time to diagnosis with systemic sclerosis
Time to diagnosis with rheumatoid arthritis
Time to diagnosis with Sjogren's disease
Time to diagnosis with psoriatic arthritis
Time to diagnosis with Raynaud's disease
Time to diagnosis with OA
Time to diagnosis with hyperthyroidism
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

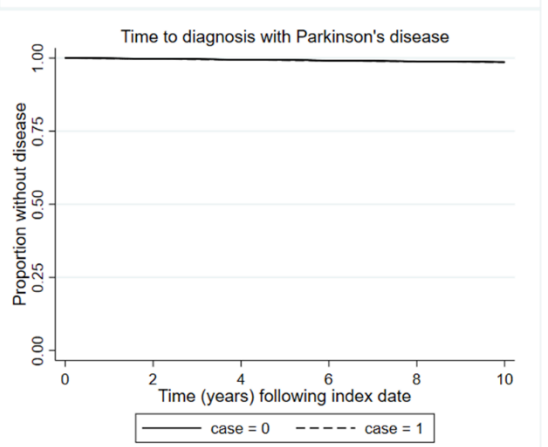

Time to diagnosis with hypothyroidism
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

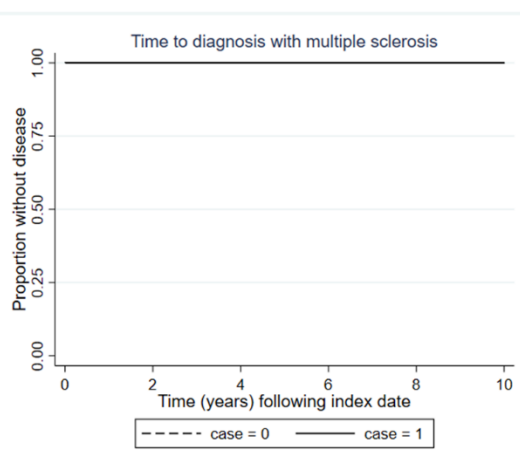

Time to diagnosis with type 1 diabetes mellitus
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

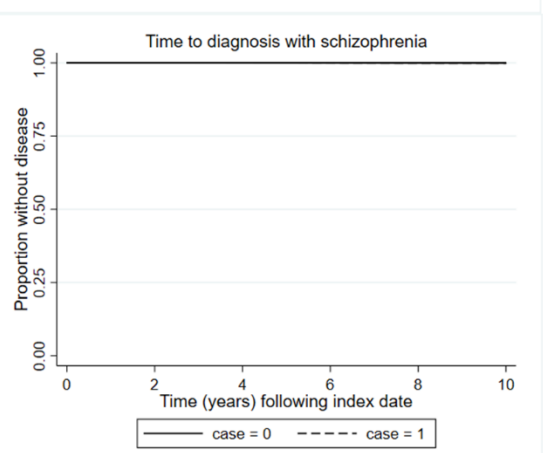

Time to diagnosis with type 2 diabetes mellitus
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

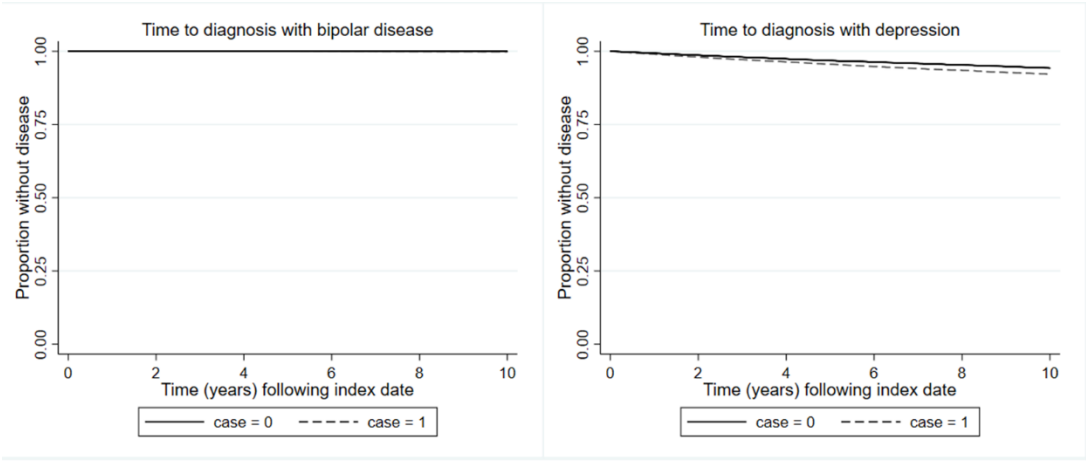

Time to diagnosis with addison's disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to diagnosis with dementia
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

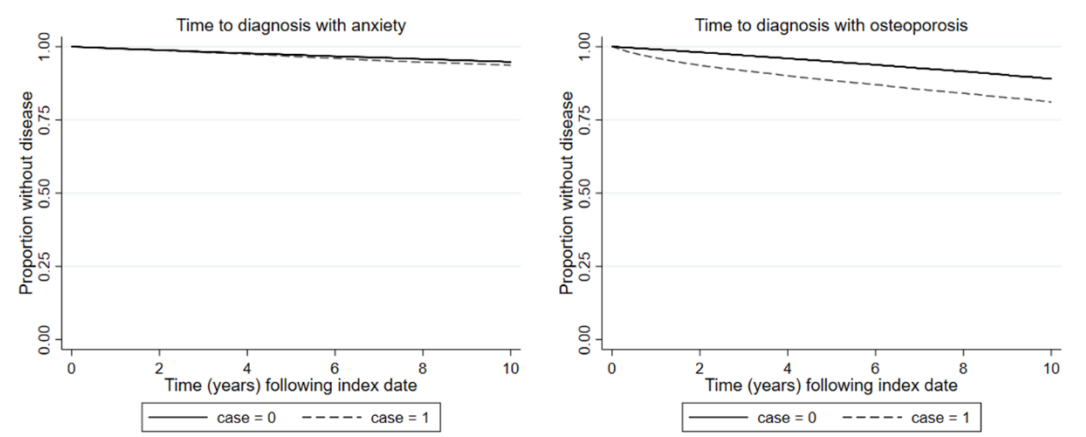

Time to diagnosis with Parkinson's disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to diagnosis with multiple sclerosis
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

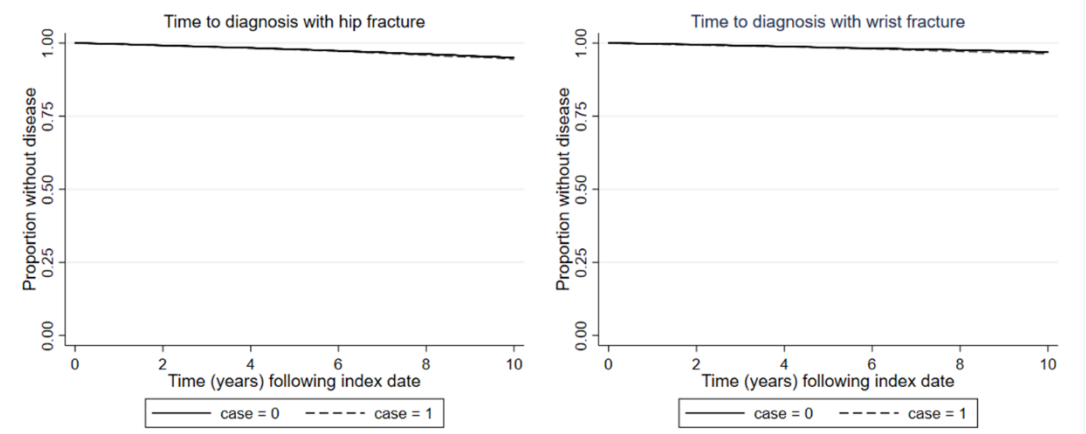

Time to diagnosis with schizophrenia
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to diagnosis with bipolar disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

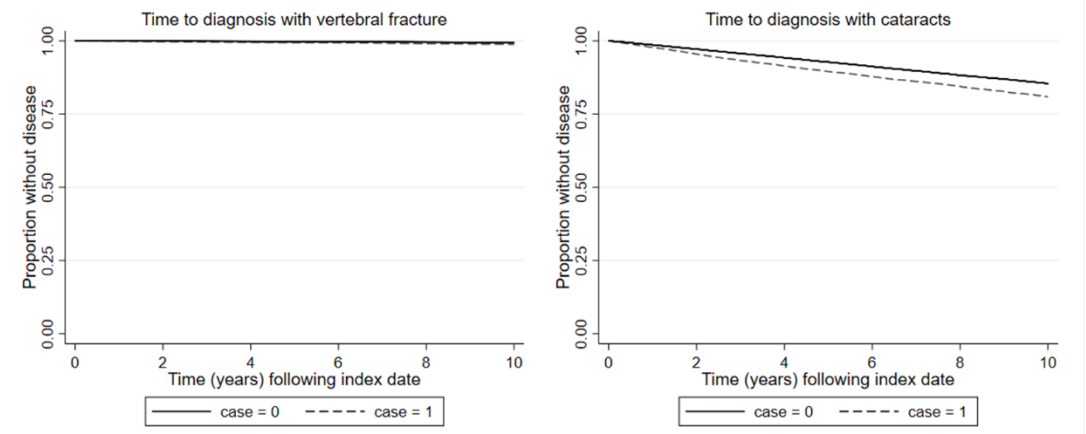
Time to diagnosis with depression
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to diagnosis with anxiety
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

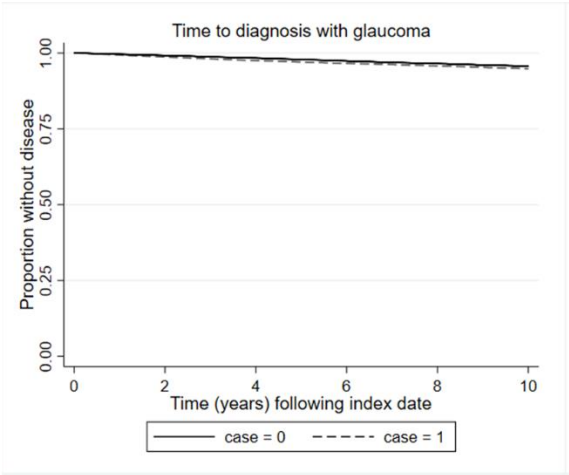
Time to diagnosis with osteoporosis
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

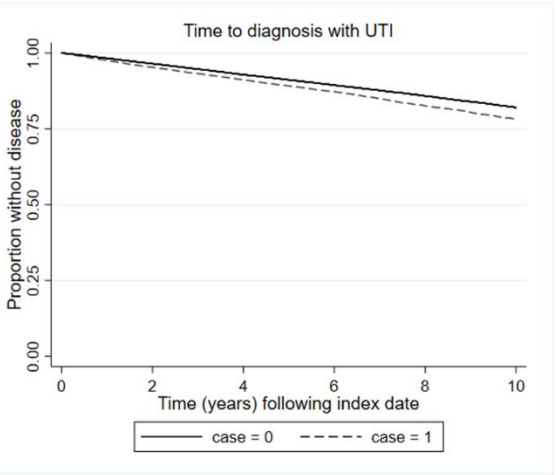

Time to diagnosis with hip fracture
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

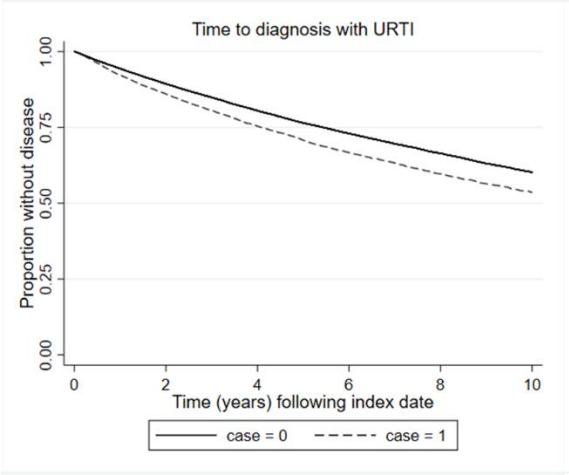
Time to diagnosis with wrist fracture
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

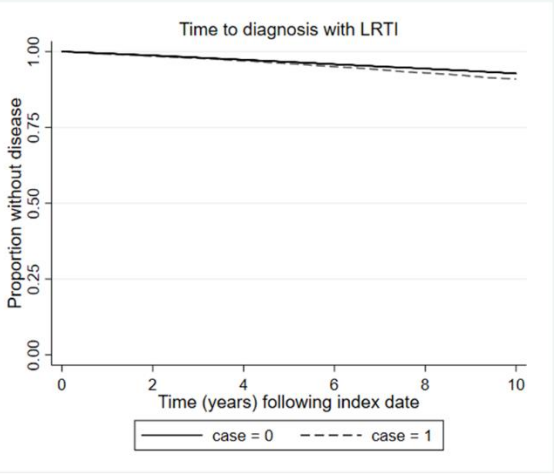

Time to diagnosis with vertebral fracture
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

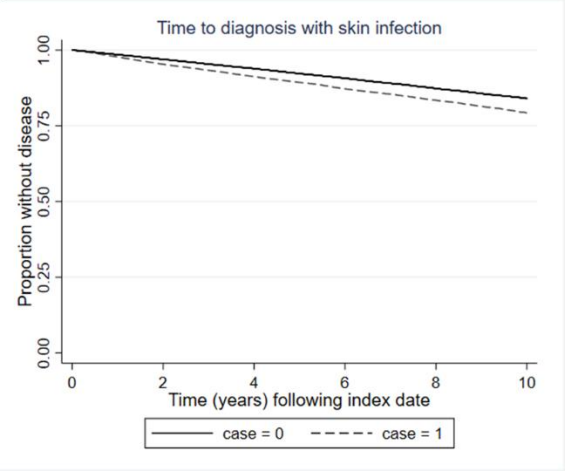
Time to diagnosis with cataracts
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to diagnosis with glaucoma
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to diagnosis with UTI
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to diagnosis with URTI
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to diagnosis with LRTI
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

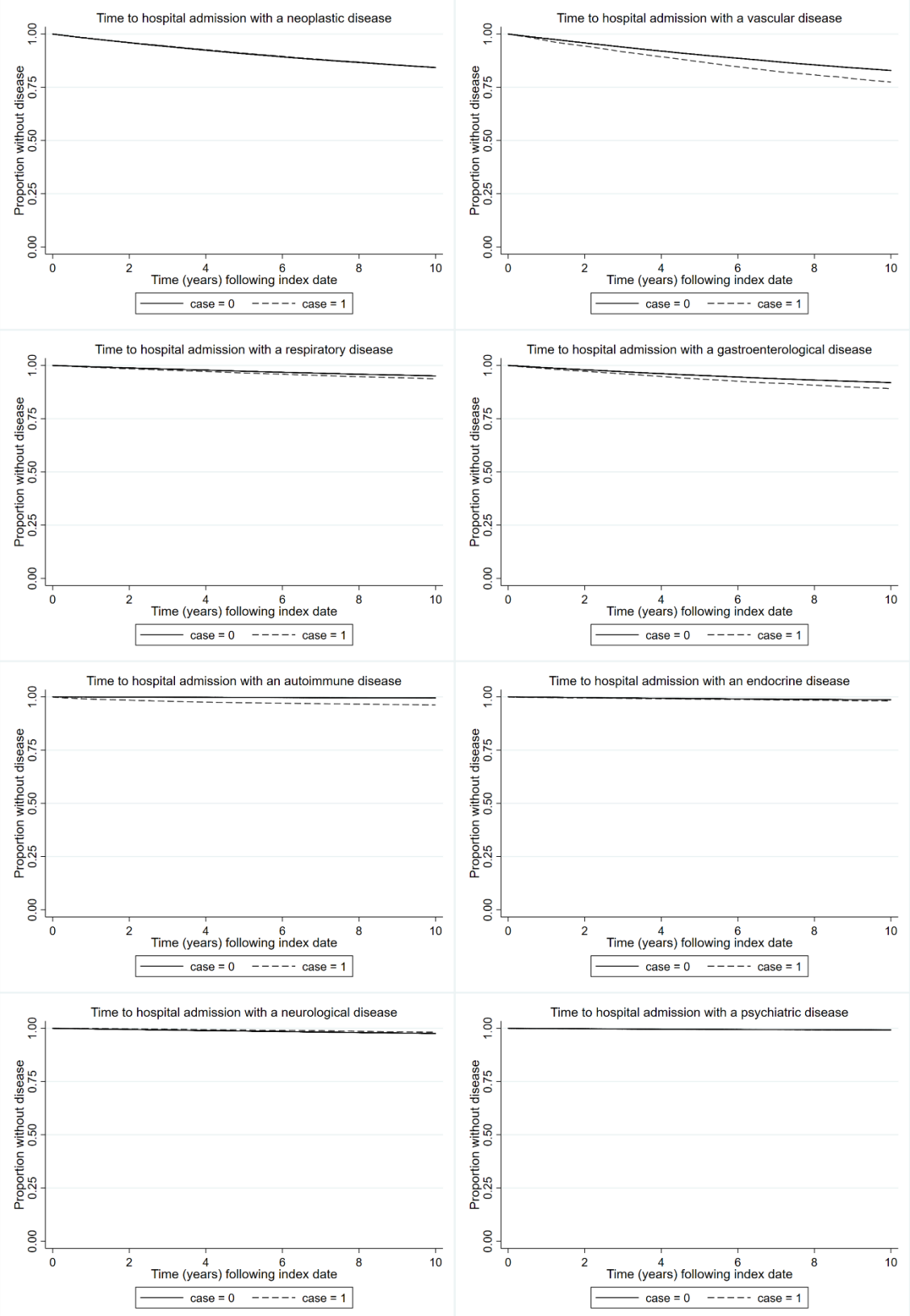

Time to diagnosis with skin infection
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

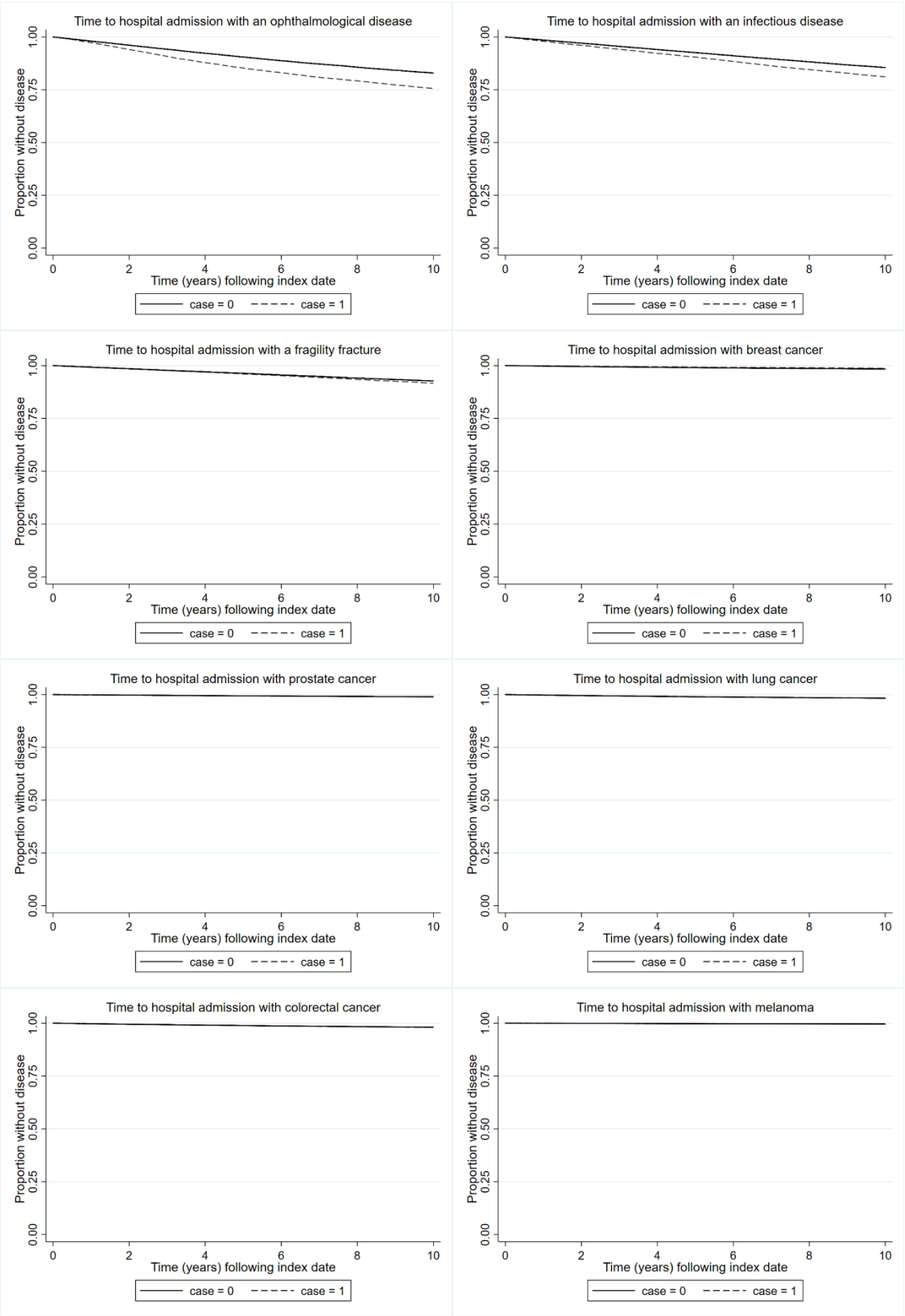
APPENDIX 7: ICD-10 codes for hospital admissions study

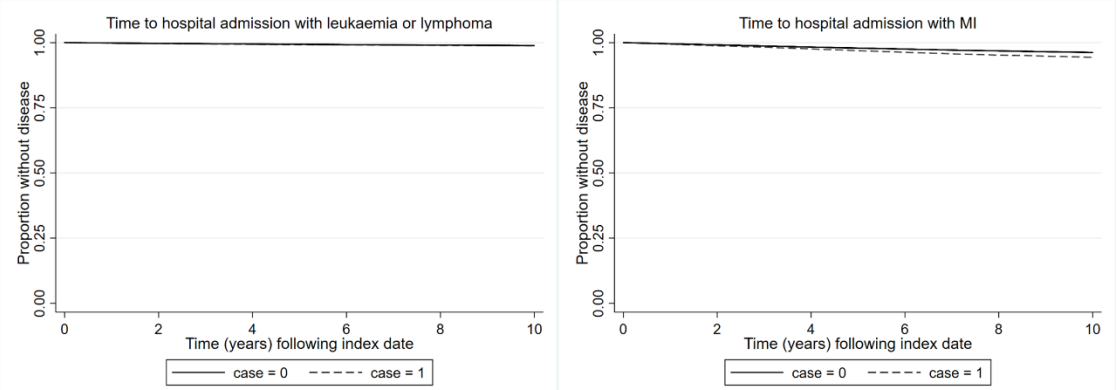
ICD-10 code	Category	ICD-10 code	Category	ICD-10 code	Category
C18	Colorectal cancer	I21	MI	J69	Pulmonary fibrosis
C19		I22		J70	
C20		I23		J84	
C21		I24		J85	LRTI
C34	Lung cancer	I50	CCF	J86	LRTI
C43	Melanoma	I51		K20	Peptic ulcer
C50	Breast cancer	I60	CVA	K21	
C61	Prostate cancer	I61		K22	
C81	Leukaemia, lymphoma	I62		K23	
C82		I63		K25	
C83		I64		K26	
C84		I65		K27	
C85		I66		K28	
C86		I67		K29	
C88		I68		K30	
C90		I69		K50	Crohn's disease
C91		I70	PVD	K51	UC
C92		I71		K70	Liver disease
C93		I72		K71	
C94		I74		K72	
C95		I77		K73	
C96		I78		K74	
E03	Hypothyroid	I79		K75	
E05	Hyperthyroid	J00	URTI	K76	
E10	T1DM	J01		K77	
E11	T2DM	J02		L00	Skin infections
F00	Dementia	J03		L01	
F01		J04		L02	
F02		J05		L03	
F03		J06		L04	
F20	Schizophrenia	J09	LRTI	L05	
F30	Bipolar disease	J10		L08	
F31		J11		M05	RA
F32	Depression	J12		M06	
F33		J13		M07	Psoriatic arthritis
F34		J14		M15	OA
F40	Anxiety	J15		M16	
F41		J16		M17	
F42		J17		M18	
F43		J18		M19	

F44		J20		M32	SLE
F45		J21		M34	Scleroderma
F48		J22		M47	OA
G20	Parkison's disease	J43	COPD	M50	
G30	Dementia	J44		M51	
G35	MS	J45	Asthma	M53	
H25	Cataracts	J46		M54	
H26		J60	Pulmonary fibrosis	M80	Osteoporosis
H27		J61		M81	
H28		J62		M82	
H40	Glauucoma	J63		N10	UTI
H42		J64		N18	CRF
I10	HTN	J65		N19	
I11		J66		N30	UTI
I12		J67		S52	Wrist fracture
I13		J68		S72	Hip fracture
I15					

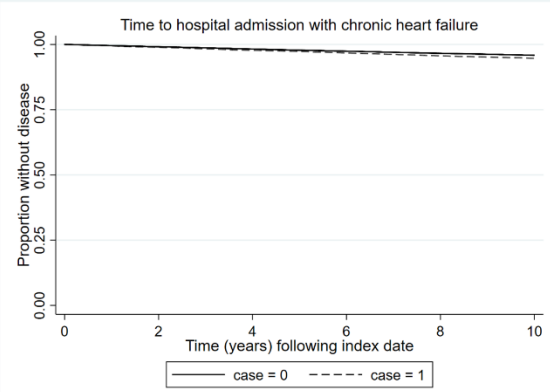
APPENDIX 8: Kaplan Meier estimates of time to admission with comorbidities

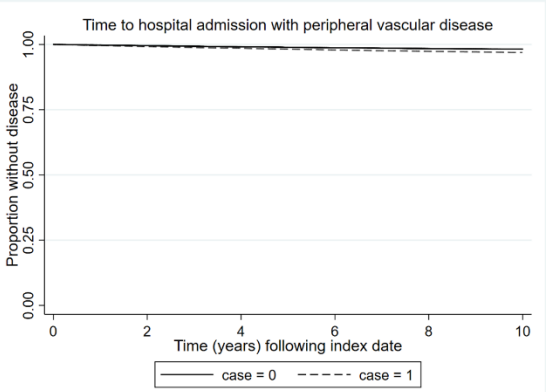


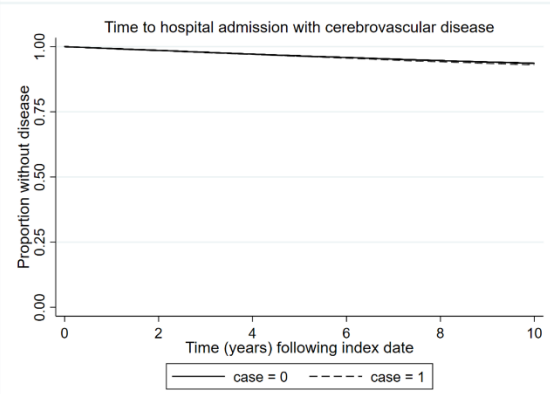

Time to hospital admission with an ophthalmological disease
Time to hospital admission with an infectious disease
Time to hospital admission with a fragility fracture
Time to hospital admission with breast cancer
Time to hospital admission with prostate cancer
Time to hospital admission with lung cancer
Time to hospital admission with colorectal cancer
Time to hospital admission with melanoma
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

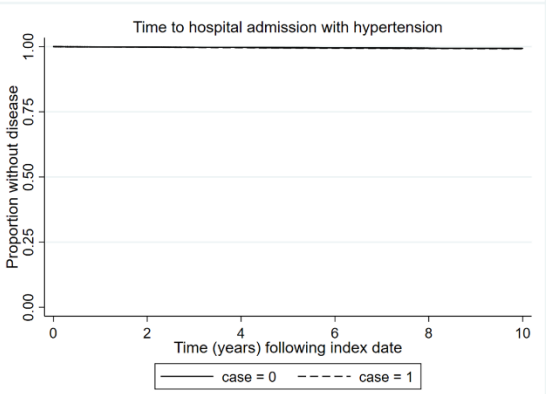

Time to hospital admission with leukaemia or lymphoma
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

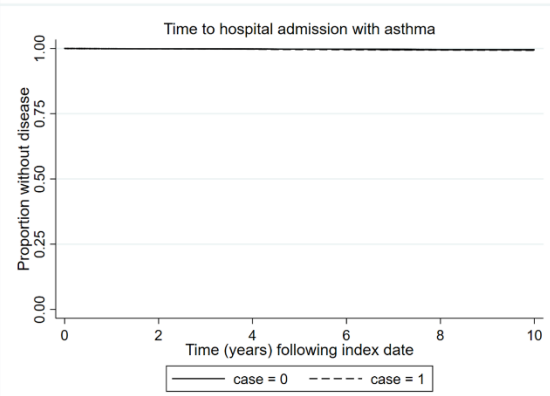
Time to hospital admission with MI
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

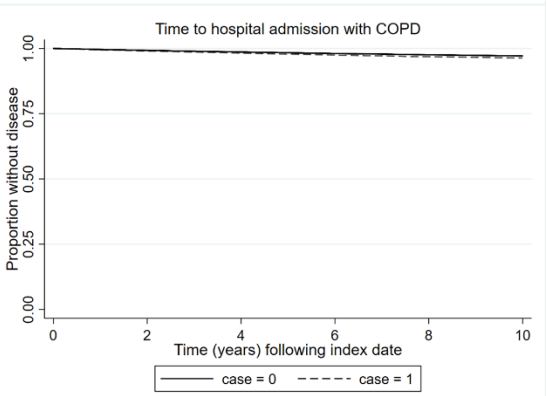

Time to hospital admission with chronic heart failure
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

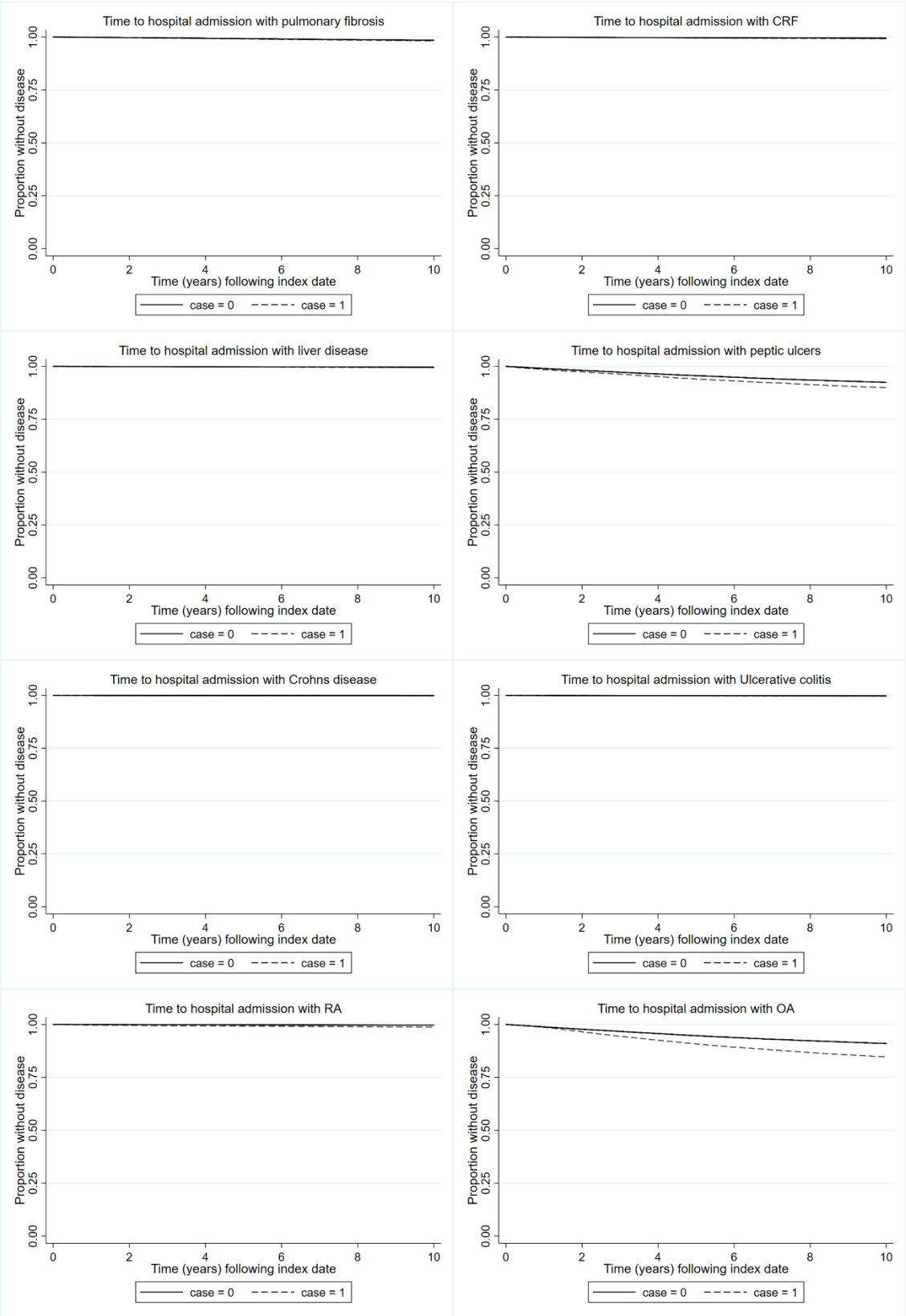

Time to hospital admission with peripheral vascular disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

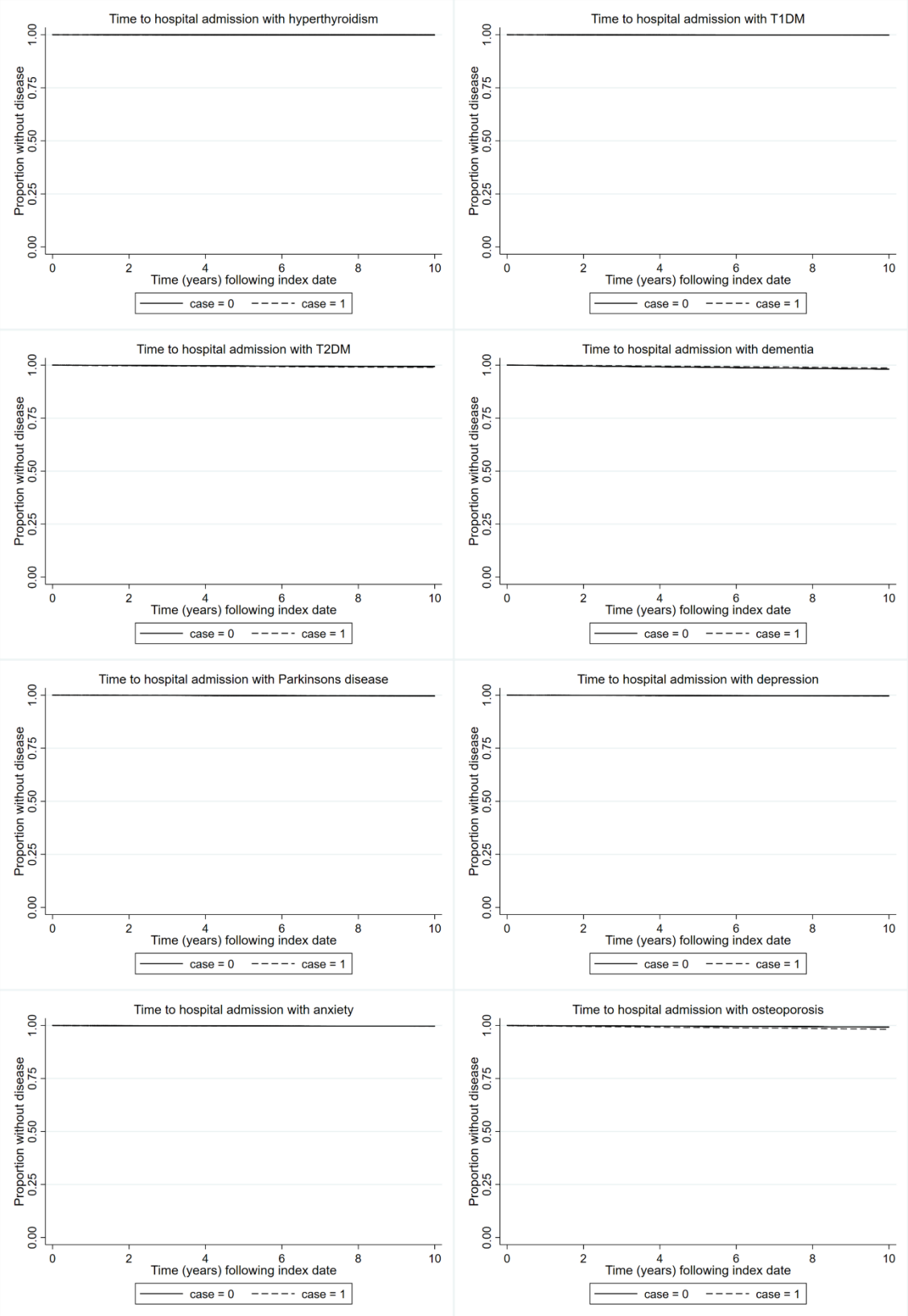

Time to hospital admission with cerebrovascular disease
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

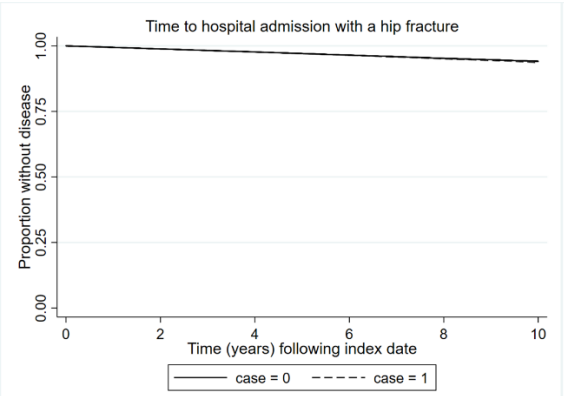

Time to hospital admission with hypertension
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

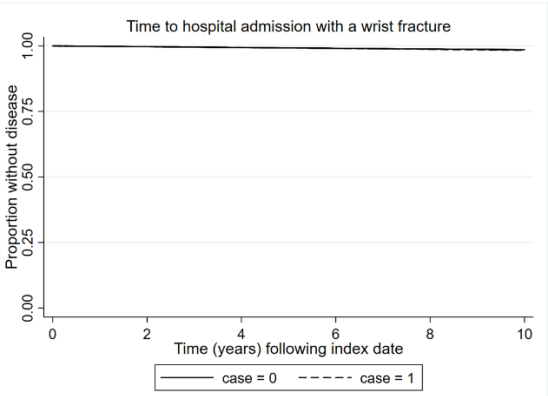

Time to hospital admission with asthma
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

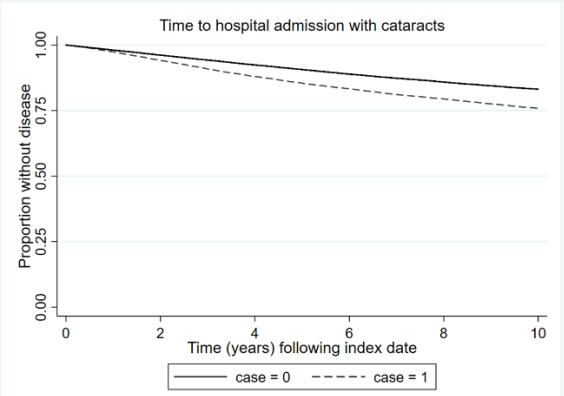

Time to hospital admission with COPD
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

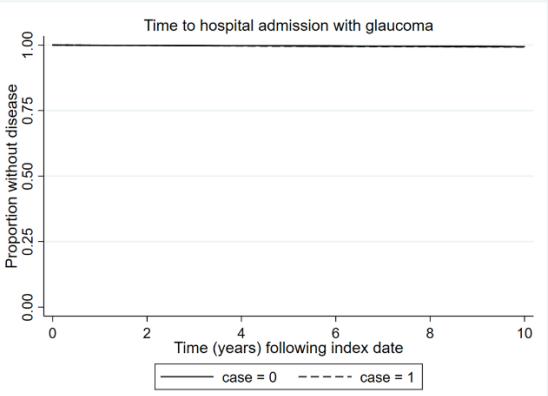

Time to hospital admission with pulmonary fibrosis
Time to hospital admission with CRF
Time to hospital admission with liver disease
Time to hospital admission with peptic ulcers
Time to hospital admission with Crohns disease
Time to hospital admission with Ulcerative colitis
Time to hospital admission with RA
Time to hospital admission with OA
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

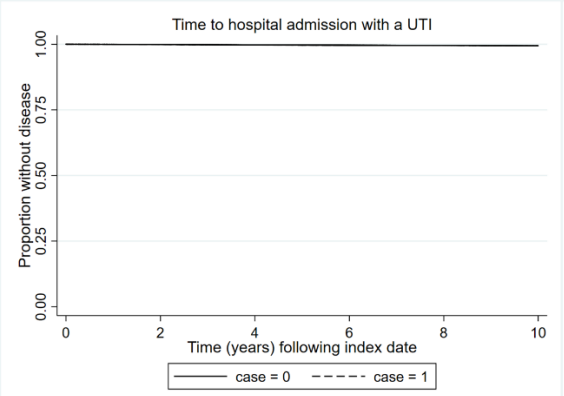

Time to hospital admission with hyperthyroidism
Time to hospital admission with T1DM
Time to hospital admission with T2DM
Time to hospital admission with dementia
Time to hospital admission with Parkinsons disease
Time to hospital admission with depression
Time to hospital admission with anxiety
Time to hospital admission with osteoporosis
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

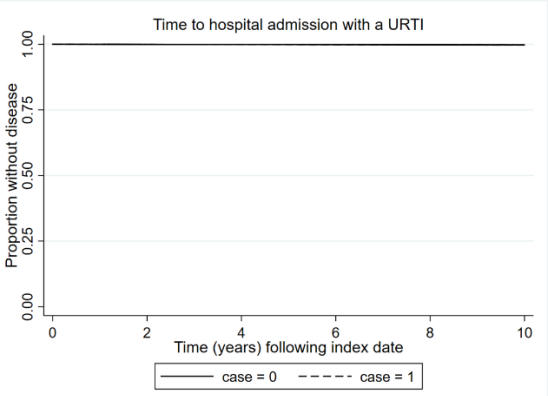

Time to hospital admission with a hip fracture
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

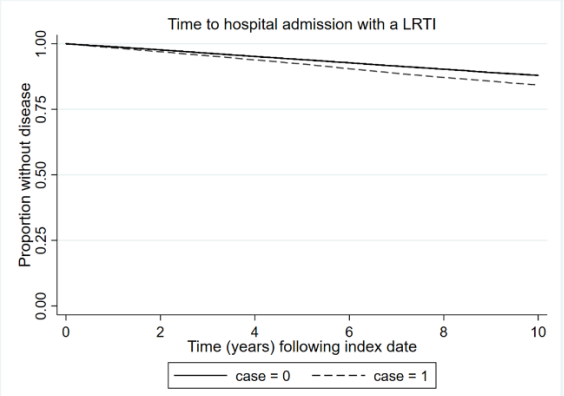

Time to hospital admission with a wrist fracture
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1

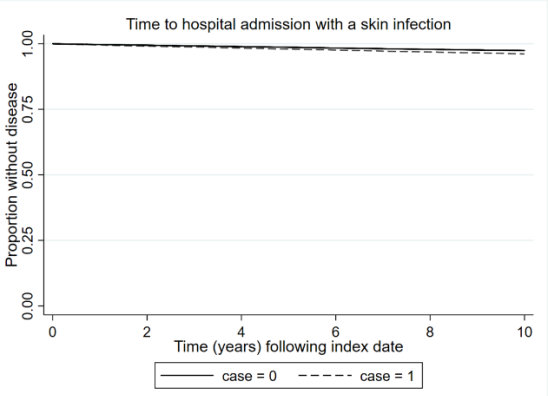

Time to hospital admission with cataracts
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to hospital admission with glaucoma
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to hospital admission with a UTI
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to hospital admission with a URTI
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to hospital admission with a LRTI
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1


Time to hospital admission with a skin infection
Proportion without disease
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years) following index date
case = 0
case = 1