RISK OF DIABETES MELLITUS ASSOCIATED WITH USE OF ORAL GLUCOCORTICOIDS IN PATIENTS WITH POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS

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"The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others."

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Contribution of other authors: SM and RW helped with the study conception, EH was a co-reviewer for the literature search and helped with data collection, RW provided guidance on the statistical analysis and all three co-authors played a crucial role in the critical review of the manuscript for content.

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ABSTRACT

Background: Oral glucocorticoid (GC) use can induce diabetes mellitus (DM). Patients with polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are both treated with GCs and can develop DM. However, it is not known whether the DM risk differs with prescribing choices such as GC dose or duration.

Objectives:

(1) To quantify DM risk associated with dose and duration of oral GC in PMR/GCA patients within the first two years of diagnosis, using Clinical Practice Research Datalink (CPRD).
(2) To explore prescribing patterns of oral GCs for PMR/GCA patients in primary care.
(3) To compare CPRD-derived prescription data with extracted data from primary care prescription data.

Methods:

(1) The impact of GC dose and duration on DM risk was explored using the extended time-varying Cox model. The additional risk associated with the timing of GC exposure was determined using the rolling cumulative dose and weighted cumulative exposure models. The risk was compared between patients on high GC dose versus low GC dose.
(2) The total monthly oral GC dose was calculated and compared with clinical guidelines.
(3) The CPRD-derived prescription data and my extracted data were compared.

Results:

(1) When compared patients on high dose versus low dose regimens, DM risk was increased by 1.4-2.5-fold within the most recent ten months for PMR patients; and 1.6-2.8-fold within the most recent five months for patients with GCA (with or without PMR).
(2) PMR prescribing was broadly in line with guidelines, but starting doses prescribed for GCA in primary care were lower than guidelines.
(3) Data from the CPRD-derived prescriptions were similar to my extracted data.

Conclusion: Higher GC dose was associated with an elevated risk of new DM in PMR/GCA patients within the initial two years of diagnosis. Treatment strategies to reduce cumulative GC dose should be investigated.

(297 words)

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ABBREVIATIONS

11β-HSD1	11β-hydroxysteroid dehydrogenase 1
95% CI	95% confidence interval
ACR	American College of Rheumatology
ACTH	Adrenocorticotropic hormone
AE	Adverse event
BAFF	B-cell activating factor
BD	Twice a day
BIC	Bayesian Information Criterion
BID	Twice a day
BMI	Body mass index
BNF	British National Formulary
BSR	British Society for Rheumatology
CBG	Capillary blood glucose
CD4+	Cluster of differentiation 4+
CDC	Centers for Disease Control and Prevention
cGR	Cytosolic glucocorticoid receptors
CHCC	Chapel Hill Consensus Conference
CINAHL	Nursing and Allied Health Literature
CPRD	Clinical Practice Research Datalink
CRP	C-reactive protein
CVD	Cardiovascular disease
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
EGP	Endogenous glucose production
EMA	European Medicines Agency
EOD	Every other day
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	US Food and Drug Administration
G6P	Glucose-6-phosphatase
GC	Glucocorticoid
GCA	Giant cell arteritis
GLP-1	Glucagon-like peptide 1
GIP	Glucose dependent insulinotropic polypeptide
GP	General practitioner
GDPR	General Data Protection Regulation

GRE	Glucocorticoid response element
HbA1c	Hemoglobin A1c
HES	Hospital Episode Statistics
HPA	Hypothalamic pituitary adrenal
HR	Hazard ratio
IA	Intra-articular
ICD	International Classification of Diseases
IL	Interleukin
IM	Intramuscular
IMD	Index of Multiple Deprivation
IQR	Inter-quartile range
ISAC	Independent Scientific Advisory Committee
JBDS-IP	Joint British Diabetes Societies for Inpatient Care
LSOA	Lower layer super output areas
Mane	Morning
MC	Mineralocorticoids
MetS	Metabolic syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTX	Methotrexate
NHS	National Health Service
NIHR	National Institute for Health Research
NLP	Natural language processing
Noct	Night
OD	Every day
OM	Every morning
ON	Every night
ONS	Office for National Statistics
OR	Odds ratio
PED	Prednisolone-equivalent dose
PEPCK	Phosphoenylpyruvate carboxykinase
PET	Positron-emission tomography
PICO	Population, Intervention, Comparator, Outcome
PMR	Polymyalgia rheumatica
PRN	When needed
QDS	Four times a day

QID	Four times a day
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SES	Socioeconomic status
SLE	Systemic lupus erythematosus
Stat	Immediately
TAB	Temporal artery biopsy
TCZ	Tocilizumab
TDS	Three times a day
THIN	The Health Improvement Network
TID	Three times a day
TNF	Tumor necrosis factor
Treg	T regulatory
Th1	Type 1 helper T cell
Th17	Type 17 helper T cell
UK	United Kingdom
USA	United States of America
UTS	Up-to-standard
WCE	Weighted cumulative exposure
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

1.1. Rationale of the PhD Project

Polymyalgia rheumatica (PMR) is a glucocorticoid-responsive condition causing bilateral shoulder and pelvic girdle pain and stiffness in older people [1, 2]. PMR is one of the commonest reasons for long-term glucocorticoid (GC) treatment in the community [3-5]. PMR is closely associated with giant cell arteritis (GCA), a common large vessel vasculitis affecting the over-50s, characterized by inflammation of the aorta, temporal arteries and other arteries supplying the arms, head and neck. Approximately one in five patients with PMR have GCA, and between 40-60% of GCA patients report PMR symptoms [6]. GCA is also treated with long-term GCs, but at higher doses [7]. The overall age-adjusted United Kingdom (UK) incidence rate of PMR is 8.4/10,000 person-years, and 1.1/10,000 person-years for GCA [8]. These incidence rates were calculated from Clinical Practice Research Datalink (CPRD), a primary care database consisting of longitudinal electronic medical records of patients registered with contributing general practices in the UK [9]. Both PMR and GCA have a female: male ratio of 2-3:1 and similar age distribution, with incidence peaking in the seventh and eighth decade of life [10]. GCs are usually prescribed at a dose sufficient to control initial symptoms, and are then tapered down over months with a typical average therapy duration of two years [11, 12]. Several studies have reported that the majority of patients with PMR and GCA experience GC-associated adverse effects [13, 14], with one of the most worrisome of these for both patients and rheumatologists being diabetes mellitus (DM) [15]. GC-induced DM is an abnormal increase in blood glucose concentration associated with GC use in patients with or without a previous history of DM [16]. Longer duration of treatment, higher GC dose and higher GC potency were reported to be associated with an increased risk of GC-induced DM [16-18]. The increase in blood glucose levels in response to GC therapy may cause an individual to become symptomatic with polyuria, weight loss, thirst and fatigue over time [19]. There is also a risk of progression to hyperosmolar hyperglycaemic state or diabetic ketoacidosis [20]. In the longer term, patients with GC-induced DM are at risk of microvascular (i.e. nephropathy, neuropathy and retinopathy) and macrovascular (i.e. cardiovascular) complications in the same way as other patients with DM. Novel adjunctive biologic therapies for GCA have been tested in clinical trials, including tocilizumab, but these biologic therapies are expensive and payers need to understand the health risks (including DM) associated with GC therapy in order to balance these against the additional costs to the payer of adding in a further drug with its associated costs. Despite the importance of this for patients, physicians and health authorities,

there is currently minimal information on what the absolute risk of DM is in these patient groups. This PhD thesis describes my work to quantify the risk of DM associated with oral GC use in PMR and/or GCA patients using the CPRD database.

1.2. Study Aims and Objectives

The overall aim was to determine what is the risk of developing new-onset DM in patients starting GC treatment for PMR and/or GCA. Within that overall aim, I systematically reviewed published literature, and also used a UK primary care research dataset to determine how that risk may vary with dose of GCs. I also wanted to investigate the time course of risk – how long after the GC therapy did the elevated risk appear to persist.

The primary objective was to model the relationship between DM risk and oral GC dose over time in newly diagnosed PMR and/or GCA patients within the initial two years of PMR/GCA diagnosis using CPRD.

The second objective was to explore the prescribing patterns of oral GCs for PMR patients, as well as GCA (with or without PMR) patients in real-world primary care settings, for which the observed prescribing patterns were compared to the prescribing recommendations in the European League Against Rheumatism (EULAR) clinical practice guidelines [21, 22].

The third objective was to compare CPRD-derived prescription data with the data that I extracted from primary care prescription data collected directly from registered primary care general practitioners (GPs) and provided by CPRD.

1.3. Outline of Thesis

The purpose of this PhD project is to develop a better understanding of the risk of DM associated with oral GC use in patients with newly diagnosed PMR and/or GCA in primary care. The risk of DM is explored and described through in-depth analysis of CPRD. CPRD is a primary care electronic medical records database consisting of clinical and prescription data linked to the Hospital Episode Statistics (HES), Office for National Statistics (ONS) mortality data and Index of multiple deprivation (IMD).

Chapter 2 provides background on the specific diseases of interest, PMR and GCA. This chapter will cover aspects such as the history, epidemiology, pathophysiology, diagnosis and classification, clinical manifestations, as well as treatment options.

Chapter 3 reviews different aspects of prednisolone, the most commonly used GC in the UK for the treatment of PMR and/or GCA. This chapter reviews the pharmacokinetic properties of prednisolone, mechanism of action, classification of conventional dosing and its relationship with both therapeutic and detrimental effects. Common GC-induced adverse events including DM will also be discussed in this chapter.

Chapter 4 is a systematic review of all published articles or conference abstracts that reported DM following exposure to oral GC therapy in patients with GCA and PMR. This chapter provides an estimate of the risk of DM in these patient populations using the random-effects model. It also provides the rationale for the importance of using large electronic health records data to better quantify the risk of DM associated with oral GC use.

Chapter 5 provides an overview of the research methods, including information regarding the prescription database and details on how the study population was constructed based on the inclusion and exclusion criteria for this study. This chapter will also address ethical considerations and use of different data sources in this study. The rationale behind use of the selected statistical methods in this project, which include the Kaplan-Meier survival analysis, extended time-varying Cox model, rolling cumulative dose model and the weighted cumulative exposure (WCE) model will also be discussed in detail.

Chapter 6 presents the baseline characteristics of PMR and/or GCA patients, stratified by disease status. Given the close overlap between PMR and GCA, there are some patients diagnosed with both PMR and GCA. Patients with both diseases are analyzed together with the GCA-only patients, as they are more likely to be receiving a similar treatment regime as those with GCA only. There are three major sections in this chapter. Firstly, the prescription data that I extracted from primary care data collected directly from registered primary care GPs across the UK will be compared with CPRD-derived prescription data managed by the CPRD team to assess agreement and discrepancies between the two datasets. A detailed analysis of the prescription database from my data extraction is also presented, covering aspects such as types of oral GC prescribed, distribution of GC dosing frequencies and duration of GC prescriptions. Secondly, the GC prescribing patterns in primary care are described and compared with EULAR guidelines. Thirdly, the risk of DM associated with oral GC dose within the initial two years of PMR/GCA diagnosis is determined using statistical methods described in the preceding chapter.

Chapter 7 discusses the findings, focusing on how the dose, duration and timing of GC treatment affects the risk of developing DM in patients with PMR and/or GCA, and how the results compare with other published literature. I also discuss the GC prescribing pattern in primary care, followed by some of the challenges associated with analyzing primary care prescription databases such as CPRD. The next sub-section includes a discussion on the strengths and limitations of the study, along with appropriate measures taken to minimize potential biases. I also discuss how my findings have implications for screening and management of DM in PMR and/or GCA patients. At the end of this chapter, the conclusions will bring together the main points from the preceding chapters to give an overview of the importance of this work, as well as outline future work.

CHAPTER 2: POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS

2.1. Overview

The content of this chapter will focus on the two central diseases of my thesis: polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). PMR and GCA are two different but frequently overlapping inflammatory disorders that often occur in patients aged 50 years and older [23]. PMR typically presents acutely with morning stiffness and bilateral shoulder pain or pelvic girdle arching [24]. GCA typically presents with persistent localised headache, weight loss, fatigue, low-grade fever, and in more severe cases, vision loss [22]. Approximately 16-21% of PMR patients are reported to have GCA [25, 26], while 40-60% of patients diagnosed with GCA also have PMR [27, 6, 28]. While the current understanding of GCA is that it is a granulomatous autoimmune vasculitis affecting larger arteries and aorta, the pathology of PMR and its overlap with GCA is unclear because of a paucity of histological data [29]. Glucocorticoids (GCs) are the cornerstone of treatment for PMR and GCA. They are highly effective and patients usually see an improvement of symptoms within 24-48 hours upon initiation of therapy [30, 31]. Oral GC therapy is known to be associated with a risk of diabetes mellitus (DM), but the actual risk in PMR and GCA is unclear. Because of the strong overlap between the two diseases, I will be looking at the risk of DM in both PMR and GCA patients. PMR and GCA are both treated with GCs, but the starting dose is much higher in GCA as this higher dose is required to control GCA symptoms whereas lower dose is sufficient in PMR. Some patients have both PMR and GCA, they are usually treated with the higher starting dose, and so because there is a strong rationale to suspect that DM risk is related to the treatment rather than the underlying disease of PMR or GCA, in studies of GC-related complications, GCA patients are usually grouped together regardless of whether they also have a diagnosis of PMR. In addition, grouping them together will also add to the robustness of statistical analyses, as they are relatively rare and infrequently encountered in primary care, with a full-time GP possibly only seeing one new case every 1-2 years [32]. In this chapter, specific areas of discussion will include a brief history, epidemiology, diagnosis and classification, clinical manifestations and treatment of PMR and GCA respectively.

2.2. Polymyalgia Rheumatica (PMR)

2.2.1. History

Polymyalgia rheumatica (PMR) was first described in 1888 as “acute senile rheumatic gout” in five elderly patients [33], and until 1950s, there were case reports describing the disease under various names, such as “periarticular fibrositis”, “peri-extra articular rheumatism”, “periarthrosis humeroscapularis” and “pseudopolyarthrite rhizomielique”. It was only in 1957 when the British physician Barber established the term “PMR” [34]. The concept of PMR was further developed by Healey, who described variant forms of PMR as “benign synovitis” [35].

Despite the establishment of the term “PMR”, the pathogenesis of the disease remains unknown, and there is considerable uncertainty regarding diagnosis and outcomes of the disease. Initial features may be variable and difficult to distinguish as approximately one in five patients with PMR have GCA [25, 26], and approximately one in two GCA patients have polymyalgic symptoms [27, 6, 28].

2.2.2. Epidemiology

PMR is almost exclusively a disease that occurs in individuals over 50 years of age, with a prevalence that increases progressively with advancing age [8]. The peak incidence of PMR is reported to be between 70 and 80 years of age [26]. Women have approximately twice the risk of developing PMR as compared to men [36, 37, 8]. Two large, observational cohort studies in Denmark and the United States of America (US) and one case control study in Norway have reported that survival in PMR patients is similar to those in the general population [36, 38, 39]. The incidence of PMR varies according to geographical regions, with countries in the northern latitudes having much higher rates. A summary of incidence rates across various countries is shown in Figure 2.1.

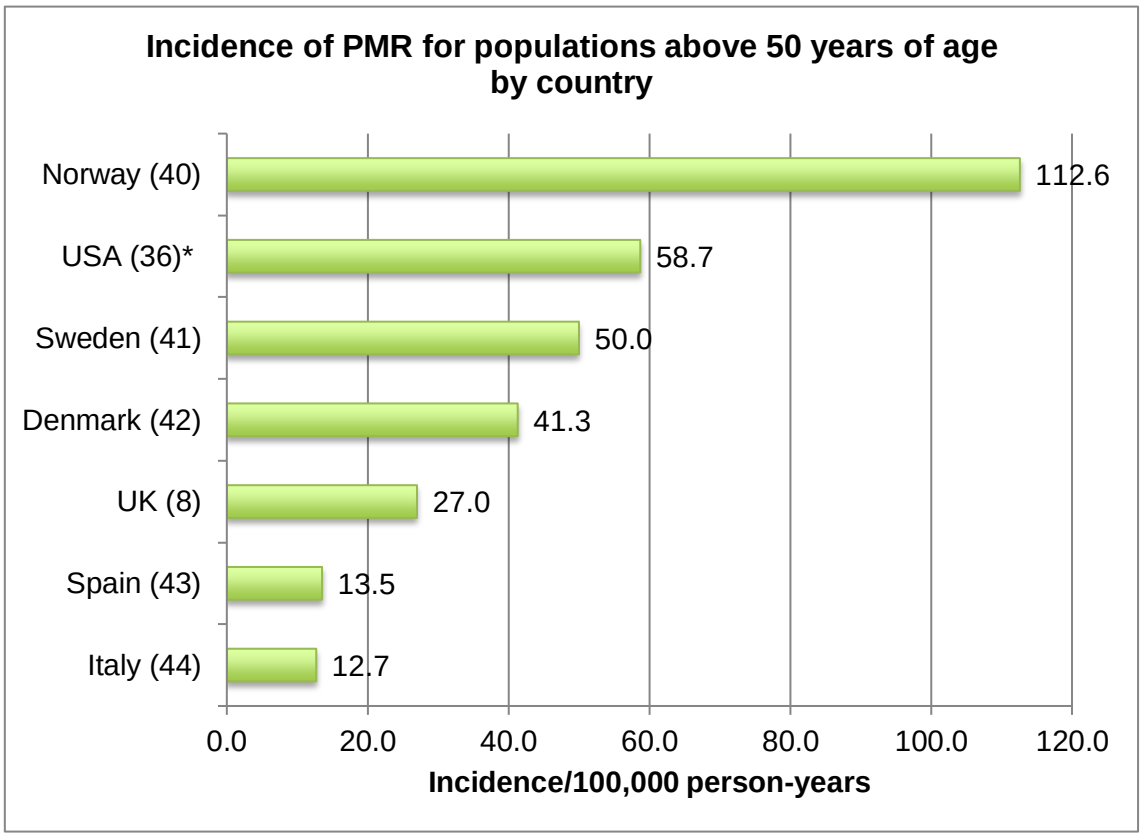

Figure 2.1: Incidence of PMR for populations above 50 years of age. Data were obtained from references [40, 36, 41, 42, 8, 43, 44].

*Note: *USA – Population was of Scandinavian descent*

2.2.3. Diagnosis and Classification

The diagnosis for PMR is a challenge as there are no established diagnostic criteria for PMR. Current guidelines recommend that the diagnosis of PMR should start with the evaluation of core inclusion and exclusion criteria, followed by assessment of the response to a standardized dose of GC [24, 21]. Core inclusion criteria include the following [24]:

- Bilateral shoulder and/or pelvic girdle pain
- Morning stiffness > 45 minutes
- Abrupt onset
- Age > 50 years
- Duration > 2 weeks
- Acute phase response (raised erythrocyte sedimentation rate (ESR)/ C-reactive protein (CRP))

Patients who present with the above-mentioned core criteria should also be screened and the following diseases - active cancer, active infection and active GCA should be excluded [24]. Next, patients should be started on oral prednisolone (15-20mg daily), and the clinical response assessed within 1 week. Patients are expected to have at least 70% global improvement by then, with elevated ESR and CRP levels normalizing within 3-4 weeks [24].

In 1979, Bird proposed the first classification criteria for PMR [45]. Two years later, Jones developed another set of classification criteria for his study [46]. This was followed by Chuang [47], who redefined a new clinical criterion for his study, which was further refined in 1984, when Healey [48] added the evaluation of steroid response to Chuang's existing criteria. A summary of the development of classification criteria over time is shown in Table 2.1.

Table 2.1: Diagnostic and classification criteria for PMR

Characteristics	***Bird, 1979 [45]***	***Jones, 1981 [46]***	***Chuang et al, 1982 [47]***	***Healey, 1984 [48]***	***Dasgupta, 2012 (EULAR/ACR) [2]***
Age onset (years)	> 65	> 50	> 50	> 50	****> 50***
Onset duration	< 2 weeks	>/= 2 months	-	-	
Signs and symptoms	• Shoulder pain and/or stiffness bilaterally • Depression and/or loss of weight • Upper arms tenderness bilaterally	• Shoulder or hip girdle pain • Morning stiffness	• Bilateral aching/stiffness ≥ 1 month involving ≥ 2 areas: neck or torso, shoulders or upper arms, hips or thighs	• Pain in the neck, shoulders or pelvic girdle • Marked morning stiffness	• ****Bilateral shoulder or pelvic girdle arching, or both*** • Hip pain or limited range of motion (1 point)
Duration of morning stiffness (minutes)	> 60	-	> 30	> 60	> 45 minutes (2 points)
ESR (mm/hr)	> 40	> 30	> 40	> 40	****Elevated***
CRP (μg/ml)	-	> 6	-	-	****Elevated***
Response to steroids	NA	-	-	Rapid response to prednisolone (≤20mg/day)	-
Other criteria	-	• Absence of rheumatoid arthritis • Absence of muscle disease	• Exclusion of other causes (e.g. active rheumatoid arthritis, lupus erythematous or polymyositis, chronic infection, multiple myeloma and Parkinson's disease)	• Absence of rheumatoid factor or antinuclear antibody	• Absence of rheumatoid factor and/or anti-citrullinated protein antibodies (2 points) • Absence of peripheral joint pain (1 point)
Number of criteria needed	≥ 3	All	All	All	Point-based (>/= 4)

*Note: * = Core criteria for PMR*

As shown in Table 2.1, the current American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) guideline recommend the use of a points-based scoring algorithm for the classification of PMR [2]. A score of ≥ 4 is categorized as PMR, with 68% sensitivity and 78% specificity; and by adding ultrasound, a score of ≥ 5 had 66% sensitivity and 81% specificity. An additional two points were allocated to the ultrasound-based algorithm – patients with at least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis and at least one hip with synovitis and/or trochanteric burtitis will be given one point. Patients who have both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis will be given another point.

Although the ACR/EULAR guideline proposed a classification criteria for PMR, they should not be used as diagnostic criteria [2]. It is essential to understand that the proposed criteria was designed as a research tool to distinguish PMR from other conditions and were not intended for the diagnosis of individual patients [49].

2.2.4. Clinical Manifestations

PMR primarily affects the muscles and joints of the shoulder, neck and hip girdles, with prominent bilateral pain and morning stiffness [50], of which the shoulders are affected in 95% of cases [47]. These symptoms usually develop over weeks to months [51], and typically are worst in the early hours of the morning or upon waking [52]. Approximately half of patients diagnosed with PMR may have distal manifestations such as hand swelling with pitting edema, peripheral arthritis and carpal tunnel syndrome [50, 43, 53, 54]. Systemic symptoms such as low-grade fever, fatigue, malaise and weight loss have also been reported between 30-50% of patients [47].

2.2.5. Treatment

GCs are the treatment of choice for PMR. In the absence of GCA, urgent GC therapy is not indicated before the clinical evaluation is complete. Patients diagnosed with PMR are typically started on 15mg of prednisolone daily and gradually tapered down over time. Initial doses of less or equal to 7.5mg/day and initial doses of greater than 30mg/day are not recommended [21]. Figures 2.2 and 2.3 show the recommended tapering regimen by the current British Society for Rheumatology (BSR) and EULAR guidelines respectively [24, 21]. For relapse cases, there is a slight difference in the recommendations between the BSR and EULAR guidelines. The EULAR guideline suggests that oral GC may be increased to the pre-relapse dose and decreased

gradually within 4-8 weeks to the dose at which the relapse occurred [21]. The BSR guideline recommends GC doses to be increased to previous higher dose, and for those with clinical features of GCA, they should be treated as GCA, usually with oral prednisolone of 40-60mg daily [24]. Single intramuscular injection of methylprednisolone 120mg can also be used [24]. Both guidelines agreed that oral methotrexate may be considered for patients on GC who are at high risk of relapse or for those who did not respond to GC treatment. Due to the heterogeneity of disease course, approach to treatment is often tailored individually depending on disease severity, co-morbidities, laboratory markers, adverse effects and patient preference. GCs are usually needed for 1-3 years [55, 24]; although some may require small doses of GCs beyond this. The 2015 ACR/EULAR guideline recommends administering GC therapies for the minimum effective duration. In terms of monitoring, the BSR guideline recommends laboratory monitoring of full blood count, ESR/CRP, urea, electrolytes and glucose levels every 3 months, in addition to monitoring in improvement of clinical symptoms. The EULAR guideline recommends individualized dose tapering and regular monitoring of PMR patients, but unlike the BSR guideline, there is no fixed schedule.

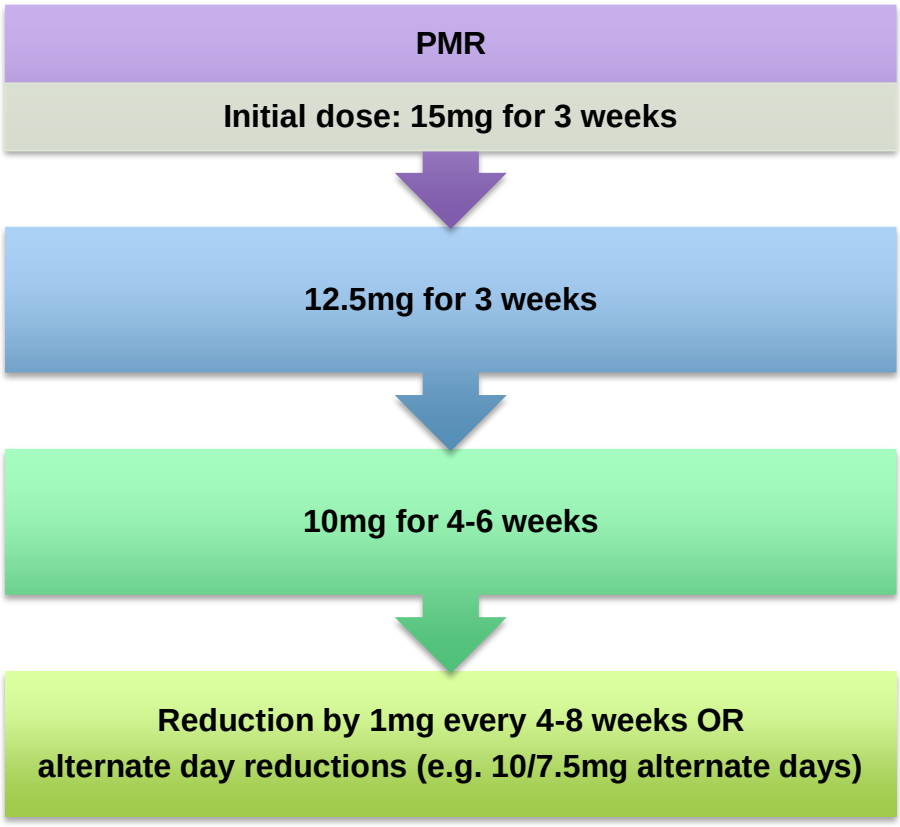

Figure 2.2: The 2010 BSR GC tapering regimen for treatment of PMR [24]

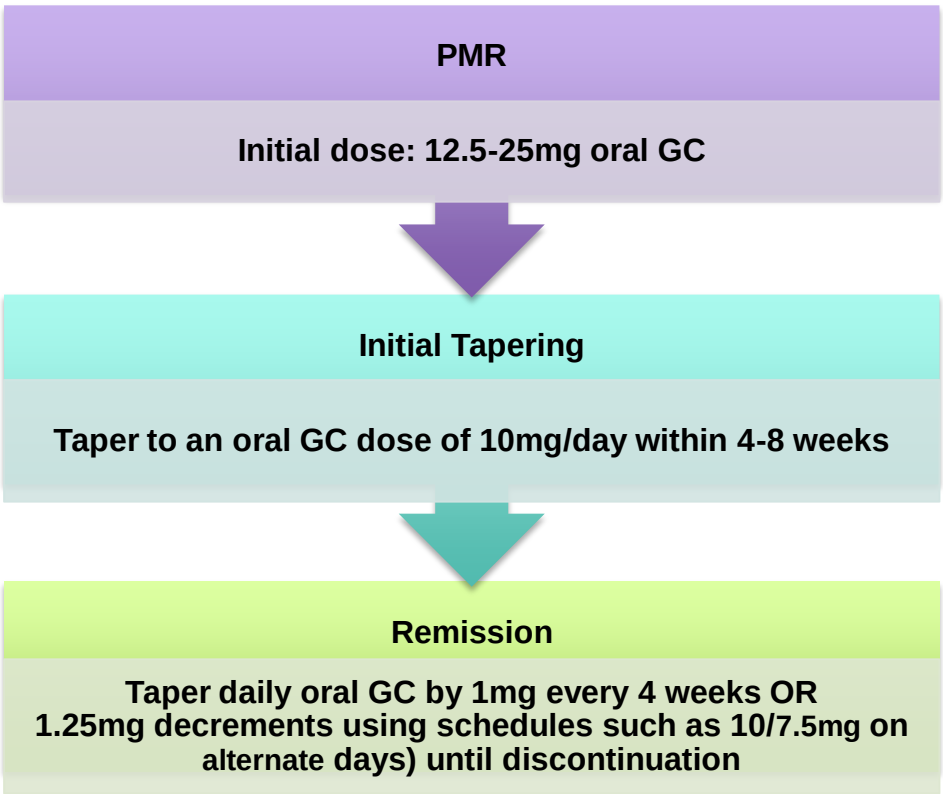

Figure 2.3: The 2015 EULAR GC tapering regimen for treatment of PMR [21]

2.3. Giant Cell Arteritis (GCA)

2.3.1. History

GCA was first described clinically in 1890 under the name “arteritis of the aged” and was later histologically characterized by Horton in 1932, which led to the name “Horton’s disease” [56]. It was also known as “arteritis temporalis” as it commonly affects the superficial temporal arteries, as well as the ophthalmic, posterior ciliary and vertebral arteries [57], while intracranial arteries are rarely associated with the vasculitic process [6]. These names were, however superseded and renamed as “giant cell arteritis” at the 1994 Chapel Hill Consensus Conference (CHCC) [58]. The presence of temporal artery inflammation was neither a required nor a sufficient feature for diagnosing giant cell arteritis, as not all patients with GCA have involvement of the temporal artery. In addition, occasional occurrence of temporal artery involvement in other forms of systemic vasculitis such as Wegener’s granulomatosis or polyarteritis nodosa also exists. In the 2012 revised version of the CHCC nomenclature, GCA was defined as a large-vessel vasculitis, affecting the aorta and its large arterial branches, with a predilection for the branches of the carotid and vertebral arteries.

2.3.2. Epidemiology

GCA is the most common type of primary systemic vasculitis affecting individuals above 50 years of age, with women being two to four times more commonly affected as compared to men [59-62]. GCA has been reported worldwide in various geographical locations among various ethnic groups. There is however, striking variation in its incidence in the different populations and regions of the world. GCA is more common in Northern European countries and among immigrants of North European descent [63-65]. Figure 2.4 summarizes the annual incidence rates among those above 50 years of age, of which the highest annual incidences were reported in Scandinavian countries, including Finland [66], Norway [67], Iceland [68], Sweden [69] and Denmark [38], followed by Mediterranean countries such as Spain [70], France [71] and Italy [44]. GCA was relatively rare among Arabs [72] and Asians [73], as depicted in Figure 2.4.

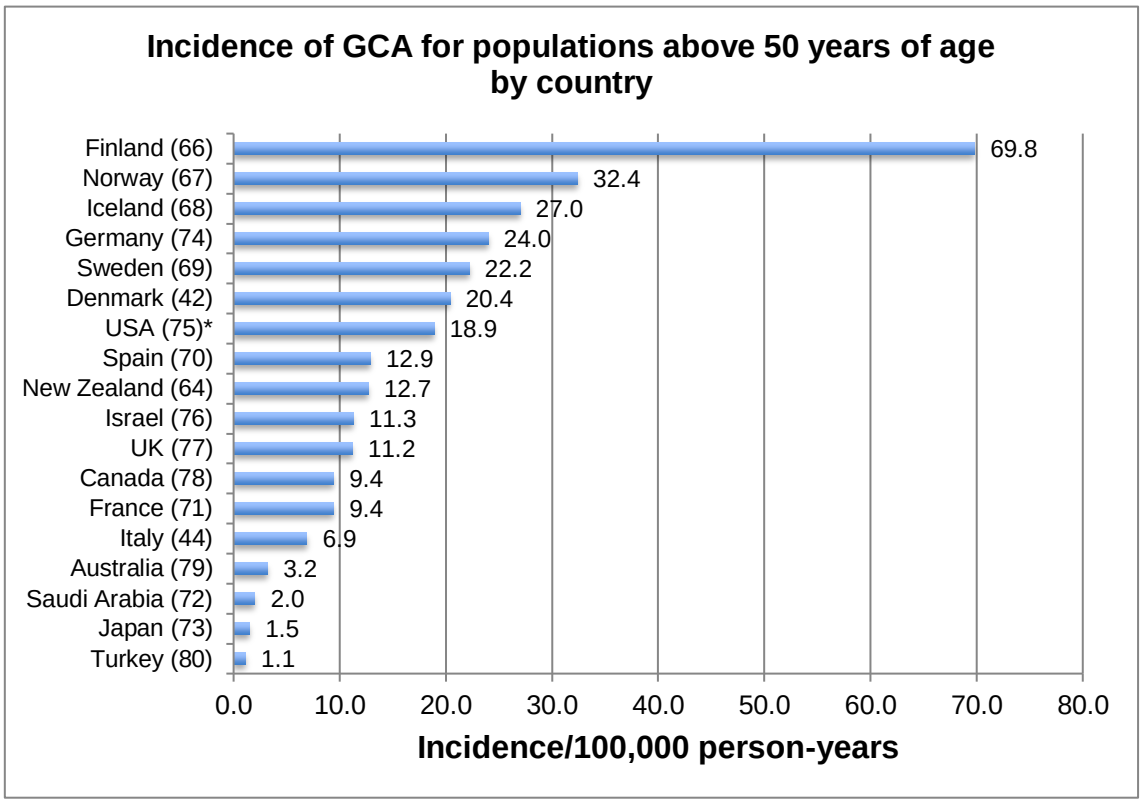

Figure 2.4: Incidence of GCA for populations above 50 years of age. Data were obtained from references [66-68, 74, 69, 38, 75, 70, 64, 76-78, 71, 44, 79, 72, 73, 80].
*Note: *USA – Population was of Scandinavian descent*

2.3.3. Diagnosis and Classification

As with PMR, the diagnosis of GCA remains a challenge, as no definitive tests for GCA exist. Ultimately, the diagnosis of GCA is made based on the clinician's experience and expertise, often based, but not confined to a combination of clinical symptoms, clinical findings, laboratory results and diagnostic imaging [81-84]. The latest BSR guideline recommends that high-dose GCs should be immediately started in patients of which GCA is strongly suspected, based on the clinician's judgment that GCA is a likely explanation for the patient's symptoms than any other condition [85]. Since GCA is a medical emergency, patients with suspected GCA should be referred urgently and be evaluated by a specialist ideally on the same working day, or at least within 3 working days [85].

Temporal artery biopsy (TAB) is the gold standard for the diagnosis of GCA. A specimen is usually taken from either one side or both left and right temporal arteries as an outpatient procedure under local anesthesia. A segment of artery (about 2.0-2.5cm long) is removed and perfusion is provided using collaterals [86]. A positive biopsy result is highly suggestive of GCA, however, it may also be seen in other forms of systemic vasculitis such as Wegener's granulomatosis, polyarteritis nodosa and rheumatoid vasculitis [87]. A recent meta-analysis reported a 77% estimated sensitivity of TAB in GCA patients [88].

Over the last years, non-invasive modalities have emerged as alternatives, which allow the arteries to be visualized noninvasively and examined for signs of inflammation. The color-coded duplex ultrasonography is able to detect the presence of a dark hypoechoic circumferential wall thickening around the lumen (also known as the "halo"), as well as the existence of stenosis and occlusions, but it requires technical skills and a high level of experience [57]. High-resolution contrast-enhanced magnetic resonance imaging (MRI) is also available to evaluate the possible inflammation of vessel walls. Other non-invasive modalities such as the positron-emission tomography (PET), which uses radioactive isotopes, have also shown to be effective for imaging inflammatory processes in GCA [86]. The use of all these imaging techniques in GCA is however, limited at the present time because of their cost and availability.

In terms of laboratory parameters, the CRP and ESR are two of the most commonly used parameters as part of the assessment of GCA. A large US population-based study, using retrospective electronic medical records from 3001 patients reported CRP levels of > 2.45mg/dL, ESR of 47-107mm/hr and platelet counts of > 400,000/mL to be the strongest laboratory predictors of a positive TAB [89]. In addition to the elevated ESR, CRP and platelet counts, normochromic normocytic anemia and an increase in acute-phase proteins on serum protein electrophoresis were also indicators of systemic inflammation in GCA patients.

In 1990, the ACR published a set of classification criteria for GCA (Table 2.2). A patient is classified as having GCA if at least three of these five criteria are present. The results have been reported to be associated with a sensitivity of 93.5% and a specificity of 91.2% when compared to patients with other forms of vasculitis [90].

Table 2.2: 1990 criteria for classification of giant-cell (temporal) arteritis [90]

Characteristics	***Definition***
Age at disease onset ≥ 50 years	Development of symptoms or findings beginning at 50 years or older
New headache	New onset of or new type of localized pain in the head
Temporal artery abnormality	Temporal artery tenderness to palpitation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
Elevated erythrocyte sedimentation rate (ESR)	ESR ≥ 50 mm/h by the Westergren method
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

The 1990 ACR classification criteria are sometimes used in clinical practice for diagnosis of GCA, this is however, inappropriate because of a few reasons. Firstly, these criteria were developed for use in clinical research and designed for a relatively homogenous cohort with typical presentations in mind, which is often not the case in clinical practice. In fact, the criteria have been reported to perform inadequately as a diagnostic tool [91, 92]. Secondly, the criteria were developed in the 1990s, long before the invention of new diagnostic techniques such as the computerized tomography and MRI that may be used to facilitate the diagnosis of GCA if available. Thirdly, the initial assumption of the ACR criteria is that the patient has systemic vasculitis, and the criteria are meant to inform the clinician whether it is GCA or not. This is often not what a clinician has in mind – in clinical practice the starting point is often a collection of symptoms that may or may not be related to systemic vasculitis [93]. In addition, symptoms may be heterogeneous in nature and differ in terms of severity, making it difficult to apply the criteria. Over the past decade, the applicability of the 1990 ACR classification in routine clinical practice has been in the limelight, and while it remains critically important in the conduct of clinical trials and epidemiologic studies with well-defined patient populations; it is not appropriate as a diagnosis tool [49].

2.3.4. Clinical Manifestations

The latest BSR guideline for the management of GCA [85] lists the following as common symptoms in GCA patients:

- Headache
- Scalp hyperaethesia
- Jaw or tongue claudication
- Temporal artery tenderness, nodularity or reduced pulsation
- Polymyalgia rheumatica (pain and stiffness of shoulder and hip girdles)
- Fever, sweats or weight loss

Less commonly, patients may also have the following symptoms [85]:

- Carotidynia
- Audiovestibular symptoms
- Dry cough
- Indications of tongue or scalp ischaemia that may precede necrosis

2.3.5. Treatment

2.3.5.1. Glucocorticoids (GC)

Glucocorticoids (GC) are the first-line treatment for GCA. In most cases, the initial dose of prednisolone ranges from 40-60mg/day. For patients with more serious symptoms such as acute or intermittent visual loss, intravenous methylprednisolone 500-1000mg/day may be given for up to 3 consecutive days before commencing oral GC [85]. In cases where intravenous therapy is not immediately possible, then oral GC should be initiated as soon as possible. The latest BSR guideline for the treatment of GCA suggests that GC dose should be tapered to zero over 12-18 months, providing there is no return of GCA symptoms, signs or laboratory markers of inflammation; and in patients at high risk of GC toxicity or those who are receiving concomitant GC-sparing therapy, a more rapid dose reduction may be implemented [85]. There is some flexibility in terms of the tapering regimen, of which emphasis was given to an individualized patient approach in the latest BSR guideline. Full assessment of the disease and co-morbidities, in addition to patient's personal priorities, should inform decisions on the tapering regimen, or if there is a need for additional treatments such GC-sparing therapies [85]. One example of a GC tapering regimen is shown in Figure 2.5. Alternative approaches may include reducing GC dose by 10mg/week in patients who are in remission above 20mg daily, and/or reducing the dose slower than stated in

Figure 2.5 in patients who are on or below 5mg daily [85]. The 2018 EULAR for the management of GCA also recommends a similar GC tapering approach to Figure 2.5, as shown in Figure 2.6. Initial doses of 40-60mg/day of GC are recommended for patients with active GCA, and if they present with GCA-related visual symptoms, then intravenous methylprednisolone 250-1000mg/day for 3 days may be considered, in addition to oral GC [22]. While the BSR guideline did not give specific recommendations on how the dose of GC should be tapered with the addition of tocilizumab (TCZ) or methotrexate (MTX) in patients with refractory or relapse GCA, the 2018 EULAR guideline included a treatment algorithm involving the use of TCZ [22]. The GC dose of patients with a major relapse may be increased to 40-60mg/day and TCZ (or MTX) may be initiated. For patients with minor relapse, GC should be tapered to the last effective dose, in addition to TCZ or MTX. With the addition of TCZ, the EULAR guideline recommends GC to be tapered to 0mg at 6 months to reduce the cumulative dose. It is however, not known if faster or conversely more prolonged GC withdrawal during TCZ therapy may lead to improved outcomes due to lack of evidence [22].

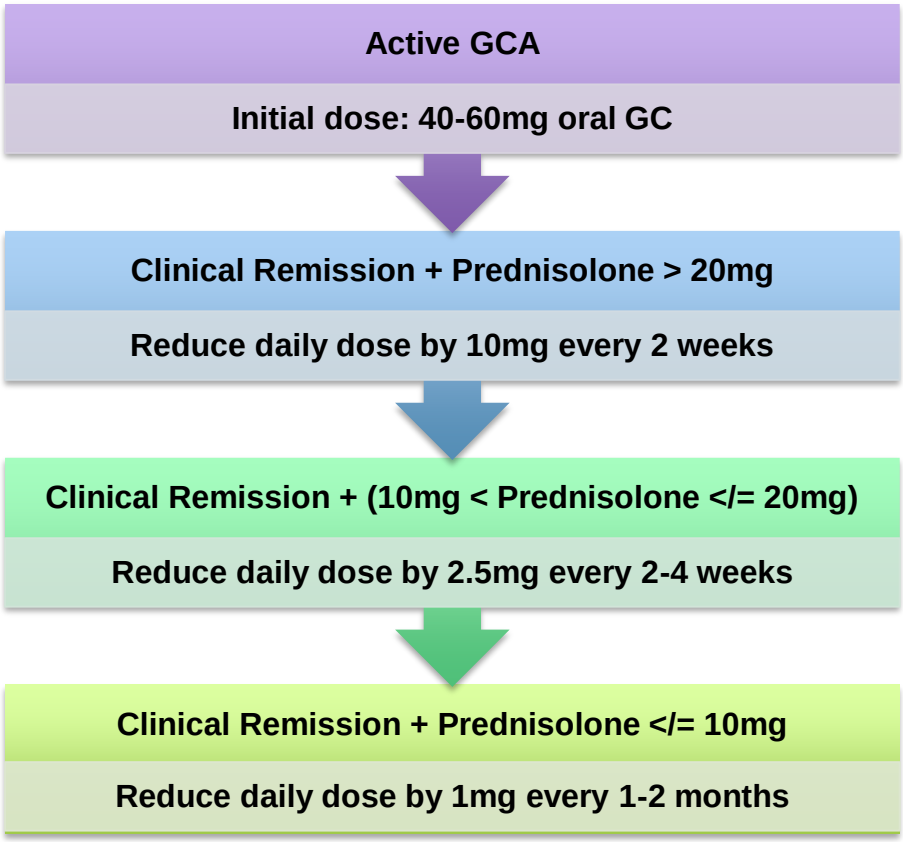

Figure 2.5: An example of GC tapering regimen for the treatment of GCA based on the 2010 BSR guideline [7]

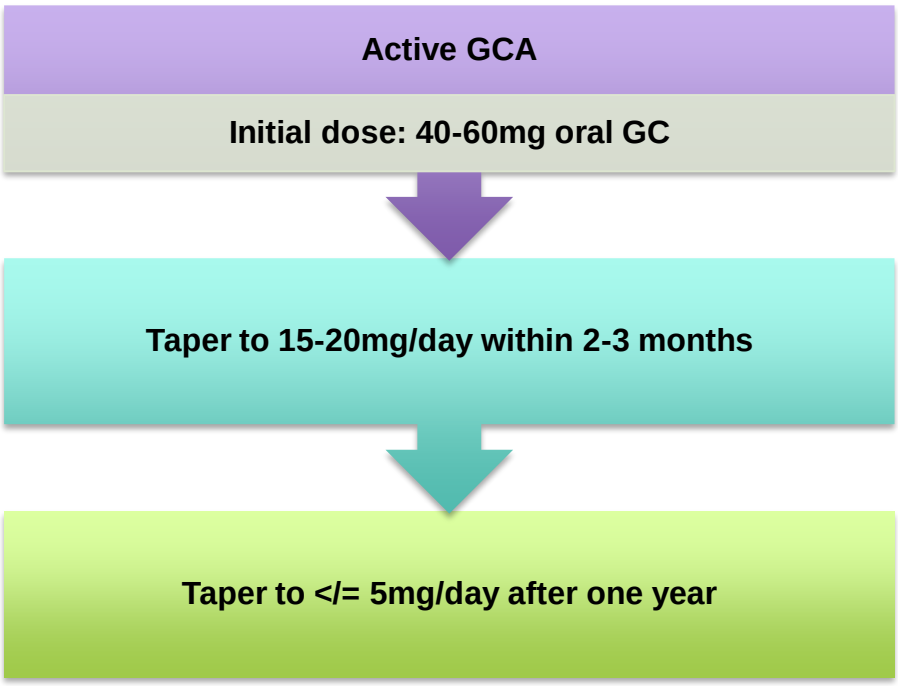

Figure 2.6: The 2018 EULAR algorithm for treatment of GCA [22]

Prompt treatment is essential to prevent irreversible complications, especially relating to blindness and stroke [94, 7]. Patients with GCA usually show a rapid improvement of clinical symptoms within 24-48 hours of treatment [95]. Laboratory measures of disease activity such as ESR and CRP usually improve substantially within a few days of therapy initiation [95].

While on GC therapy, patients should be regularly monitored for treatment efficacy, as well as safety. Laboratory monitoring of inflammatory markers such as full blood count, CRP and ESR (or plasma viscosity if ESR is unavailable) is highly recommended before or immediately after the initiation of high-dose GC. Baseline laboratory tests of major organ system function, including renal and liver function tests, calcium and alkaline phosphatase should also be monitored [85]. Since GC use is reported to be associated with numerous adverse events [96, 97], the BSR guideline recommends patients to be evaluated for hypertension and hyperglycaemia within the first two weeks of GC therapy initiation, as well as consider appropriate bone protection such as calcium and vitamin D, with oral biphosphonate if not contraindicated.

2.3.5.2. Biologic Agents

Several studies looked at the efficacy of several biologics as adjuvant therapy. Tocilizumab (TCZ) is a biologic that was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of GCA in 2017, based on the efficacy shown in two randomized clinical trials (RCT). One RCT [98] demonstrated increased rates of remission (85% vs. 20%) at 52 weeks, in addition to significantly lower mean cumulative GC dose in the TCZ group (43mg/kg vs. 110mg/kg). Another RCT [99] also demonstrated increased rates of remission (53-56% vs. 14-18%) at 52 weeks, with significant lower median cumulative GC dose among TCZ patients (1862mg vs. 3818mg). TCZ is also shown to be more cost-effective for patients with relapsing or refractory disease. When compared with GC alone, the cost-effectiveness estimated was £24,977 per quality-adjusted life year gained, assuming that patients receive TCZ for one year at most, and this was within the range normally considered to be a cost-effective use of National Health Service (NHS) resources [100]. The latest 2019 BSR guideline recommends TCZ to be used in combination with a GC taper for patients with relapsing disease, or for those at high risk of developing GC toxicity [85].

Ustekinumab is a monoclonal antibody, and it is one of the newest agents whose use is being explored in the treatment of GCA. In an open-label study of 25 patients with refractory GCA, the mean GC dose was decreased from a median of 20mg/day to 5mg/day at week 52 and six patients (24%) discontinued GC therapy entirely [101]. A current RCT is being carried out among patients with refractory or relapsing GCA, and recruitment is expected to complete in 2023 [102].

Three tumor necrosis factor (TNF) antagonists – infliximab, adalimumab and etanercept were found to be ineffective in the treatment of GCA, based on the results of three RCTs. The infliximab study was terminated early, as the proportion of patients on infliximab without relapse at 22 weeks did not increase as compared to placebo (43% vs. 50%, p=0.65). The proportion of patients whose GC dosages were tapered to 10mg/day without relapse was also not higher than placebo (61% vs. 75%, p=0.31) [103]. For the adalimumab study, results showed that the addition of adalimumab to GC did not increase the number of patients in remission at six months, as compared to placebo (59% vs. 50%, p=0.46) [104]. The etanercept study was a small single-centre RCT, of which the results showed that 50% of etanercept-treated patients were able to control disease activity without GC at the end of 12 months, as compared to 22% in the placebo group. This was however, not statistically significant. Etanercept-treated

patients also had a lower cumulative GC dose at 1 year as compared to placebo patients (1.5g vs. 3g, p=0.03), though the limited number of patients (n=17) makes it impossible to draw definitive conclusions.

The role of abatacept, a biologic that blocks the activity of T-cells, has also been explored in a small RCT. Trial results demonstrated modest improvements in relapse free survival (48% vs. 31%, p=0.049) at 12 months and longer median duration of remission (9.9 months vs. 3.9 months, p=0.023) in abatacept-treated patients [105]. To date, there is however, insufficient evidence to support its use in the treatment of GCA.

2.3.5.3. Methotrexate (MTX)

Three RCTs comparing low dose MTX with placebo in patients with GCA treated with GCs had divergent conclusions – two of the trials showed no effect [106, 107], whereas one reported reduced relapse rates and lower GC doses with the addition of MTX [14]. A meta-analysis of the individual patient-level data of 161 patients from these RCTs [108] suggested that the use of MTX as adjunct therapy resulted in a lower relapse rate, the need for lower GC cumulative dose and a higher rate of GC-free remission, but there was no difference in adverse event rates. The latest BSR guideline [85] and 2018 EULAR guideline for the treatment of GCA [22] suggests that MTX might be considered for GCA, in combination with a GC taper, in patients at high risk of GC toxicity or those with relapse.

2.3.5.4. Aspirin

To date, there are no RCTs published on the use of aspirin in GCA. A Cochrane systematic review was done in 2014, looking at the safety and efficacy of aspirin as an adjunctive treatment in GCA, of which the authors concluded that there was insufficient evidence to justify the use in routine clinical practice [109].

2.3.5.5. Other Immunosuppressants

One small RCT showed that azathioprine of 150mg/day demonstrated a significant reduction in mean GC dose over 52 weeks, as compared to those in the placebo group (1.9mg/day vs. 4.2mg/day at the end of 52 weeks, $p<0.05$) [110]. The study, however only had 31 patients enrolled, of which 7 of the azathioprine-treated (44%) withdrew from the study due to azathioprine related side effects.

A few small studies have suggested that cyclophosphamide may be useful in GCA patients at high risk of GC-related adverse effects [111-113]. A systematic review identified 88 patients who received cyclophosphamide, of which 74 (84%) were responsive to cyclophosphamide and only 17 (19%) had a relapse. It is worth noting though, that all the patients were receiving a maintenance therapy with other immunosuppressive agents such as MTX, of which the true effect of cyclophosphamide would have been confounded by the effect of another drug.

The potential of cyclosporin A as adjunctive therapy in the treatment of GCA was also explored in two randomized open-label studies [114, 115], of which the authors reported that cyclosporin A did not demonstrate a significant steroid-sparing effect.

The potential of other immunosuppressants such as leflunomide [116], mycophenolate mofetil [117] and dapsone [118] as a GC-sparing agent in GCA have been explored, but there is insufficient evidence to support their use as they were all case series or retrospective studies. It is therefore, not routinely used in clinical practice due to the lack of evidence in terms of safety and efficacy.

While there is no known cure for PMR and GCA, these diseases can be treated and controlled. As mentioned in this chapter, GC is the cornerstone of therapy. I will be discussing the role of GC in detail in the next chapter.

CHAPTER 3: GLUCOCORTICOIDS

3.1. Overview

Cortisone, the first steroid, was first discovered in 1929 by a group of scientists who prepared extracts from the adrenal cortex that successfully controlled symptoms of adrenal insufficiency in patients with Addison's disease [119]. Cortisone was eventually developed into a chemical compound and was first used in 1949 for the treatment of rheumatoid arthritis [120]. Nearly seven decades later, the clinical use of steroids has expanded greatly, mainly due to their potent anti-inflammatory and immuno-modulating properties. The term "steroid" applied to a wide range of molecules with varying physiological effects, including mineralocorticoids (MCs) and glucocorticoids (GCs). MCs such as aldosterone play a critical role in the regulation of sodium and water transport [121]. Naturally-occurring GCs are part of the feedback mechanism that the body utilizes to reduce inflammation, while exogenous GCs are used to treat diseases caused by an overactive immune system, including, but not limited to respiratory diseases, autoimmune diseases and rheumatic diseases. GCs have been used for the treatment of both polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) since the 1960's, and to date, they are still the cornerstone treatment for both these diseases. GCs are like a double-edged sword - while they are considered "the miracle or wonder drug" for most patients due to their effectiveness in the rapid amelioration of symptoms, they are also harmful, and clinicians often need to deal with the dichotomy that GCs can both treat and harm patients. One report published by the PMRGCAuk group (a registered charity in Great Britain, established by a group of patients and clinicians) adopted the metaphor of "fighting a dragon" when dealing with GC use in PMR and GCA [122]. A dragon has a fiery head, a long spiny back, and a sting in the tail. At the point of diagnosis, patients struggle with acute pain and discomfort, and while GCs deal with this crisis period, it is followed by the challenge of managing the balancing act between GC dose titration and re-emergence of acute symptoms, as well as having to deal with the short to medium term adverse effects [122]. Once they have tapered GCs to a minimum (the dragon's tail), they are faced with the long-term complications of GC therapy such as diabetes mellitus (DM). While this thesis will not be the ultimate solution for this daunting problem, it is hoped that the results would shed some light on the management of GC-induced DM. Since GCs are the main exposure in my thesis, this chapter will discuss in detail the pharmacokinetics and mechanism of action, followed by the definition of conventional terms for GC doses. The last section of this chapter will include a discussion on GC-induced DM.

3.2. Pharmacokinetics

The hypothalamic pituitary adrenal (HPA) axis is a complex set of interactions between the hypothalamus, pituitary gland and adrenal gland. The adrenal gland secretes steroid hormones essential for the regulation of stress response, blood pressure and volume, fluid and electrolyte balance, and inflammation. The HPA axis involves the stimulation of adrenocorticotropic hormone (ACTH) release from the pituitary by the hypothalamus. Elevated blood levels of ACTH in turn stimulate the zona fasciculata in the adrenal cortex to produce cortisol, a hormone essential for the utilization of carbohydrates, fat and protein, as well as maintaining energy homeostasis during stress [123].

Synthetic GCs mimic the effects of cortisol and are the first class of endogenous anti-inflammatory mediators that have been successfully used for therapy purposes. The two most common GCs are prednisolone and prednisone. They were introduced into clinical practice in the 1960s, with prednisolone being primarily prescribed in the UK, and prednisone in the US. Prednisolone is an active steroid, while prednisone is a prodrug that is converted by the 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) to the active metabolite prednisolone in the liver after administration. Prednisolone is well absorbed from the gastrointestinal tract after oral administration and is known to moderately bind to the corticosteroid binding globulin (i.e. glycoprotein transcortin) and albumin in a non-linear manner [124-126]. Several pharmacokinetic studies have shown that the unbound fraction of prednisolone accounts for its biological effect, rather than the total serum drug concentration [127-129]. In other words, only the free drug that reaches the site of action and interacts with the receptor is biologically relevant; and since it exhibits non-linear binding properties, the dose-response relationship is also non-linear [130]. The plasma half-life after oral administration of prednisolone is between 3 to 4 hours, depending on the dose [131, 132].

3.3. Mechanism of Action

The host inflammatory response is a primary defence mechanism that is immediately activated in response to any infection or injury. There are two types of responses, namely the innate and adaptive immune systems [133]. The innate immune system is the first line of defence in acute inflammation, primarily composed of cells that serve as a barrier function and phagocytes recruited early to sites of pathogen invasion. It is relatively non-specific and provides a rapid reaction to infections or injuries. The adaptive immune system, on the other hand, consists of lymphocytes and antibodies that plays a major role in chronic inflammatory disease, provides a highly antigen-specific response, and develops much later in the host inflammatory response. GCs inhibit many of the initial events in an inflammatory response. They promote the resolution of inflammation by the following mechanisms: firstly, inhibiting vasodilation and therefore prevent the increase in blood flow; secondly, preventing increases in vascular permeability, thereby reducing exudate formation; and thirdly through the suppression of leukocyte emigration [134].

3.3.1. Genomic Mechanisms

A few studies have proposed two types of mechanisms that inhibit events of the inflammatory and immune response – genomic and non-genomic [135-137]. Genomic effects are mediated by cytosolic glucocorticoid receptors (cGR). These receptors are members of the steroid hormone receptor family, which is a superfamily of ligand-inducible transcription factors. When administered, the lipophilic GCs will bind to the ligand-binding domain of the cGR with high affinity, which in turn results in activation of the receptor and disassociation of the receptor from the multiprotein complex [138]. Nuclear translocation of the GC-cGR complex occurs within 10-30 minutes of cell exposure to GC, which will then bind to DNA binding sites called the glucocorticoid response elements (GREs) [138]. The GC-cGR complex will then activate the transcription of anti-inflammatory factors (e.g. interleukin-10, annexin 1 and inhibitor of nuclear factor κB), as well as regulatory proteins [139]. This process, which is thought to be responsible for numerous adverse effects of GCs, is called transactivation [140]. Another mechanism of action is transrepression, which describes the ability of the GC-cGR complex to inhibit the transactivation function of transcription factors such as activator protein 1 and nuclear factor κB [141, 142]. It has been suggested that the anti-inflammatory and immunosuppressive effects of GCs are induced by genomic transrepression, by which synthesis of proinflammatory mediators such as the interleukin-1 (IL-1, IL-2, tumor necrosis factor, interferon gamma and prostaglandins

are suppressed [140, 143]. These genomic effects occur at any therapeutically relevant dosage, and are generally slow due to the time-consuming process of messenger ribonucleic acid (mRNA) transcription and translation. The degree of cytosolic receptor saturation is considered as a direct modulator of the intensity of therapeutic anti-inflammatory and immunosuppressive GC effects [144]. Some of the anti-inflammatory and immunosuppressive effects (e.g. rapid clinical response to administration of high dose intravenous GC), however, occur too rapidly to be explained by this genomic mode of action, therefore it is likely that non-genomic mechanisms are also involved [137, 145, 146].

3.3.2. Non-genomic Mechanisms

As outlined above, some GC responses do not fit the classical genomic model of GC action due to its rapid occurrence in response. Losel and Wehling defined non-genomic mechanisms as any action that does not affect gene expression initially or directly, but rather drives more rapid effects such as the activation of signaling cascades [146]. The following non-genomic effects of GCs have been studied and documented [147]:

- GCs exert rapid effects on intracellular calcium homeostasis and agonist-induced calcium mobilization
- GCs rapidly modulate skeletal and smooth muscle function
- GCs exert rapid effects on reactive oxygen species / reactive nitrogen species
- GCs exert rapid effects on inflammatory and apoptotic pathway

There are many factors that affect the clinical response of GCs, including the rate of absorption, concentration in the target tissues, affinity of GC to the GC receptors, rate of metabolism and rate of clearance, as well as the dose administered, as GC effects are strongly dose-dependent [148]. Figure 3.1 summarizes the occurrence of genomic and non-genomic effects in terms of a dose-response relationship [135, 136, 149, 144] that will be further discussed in Section 3.3.3.

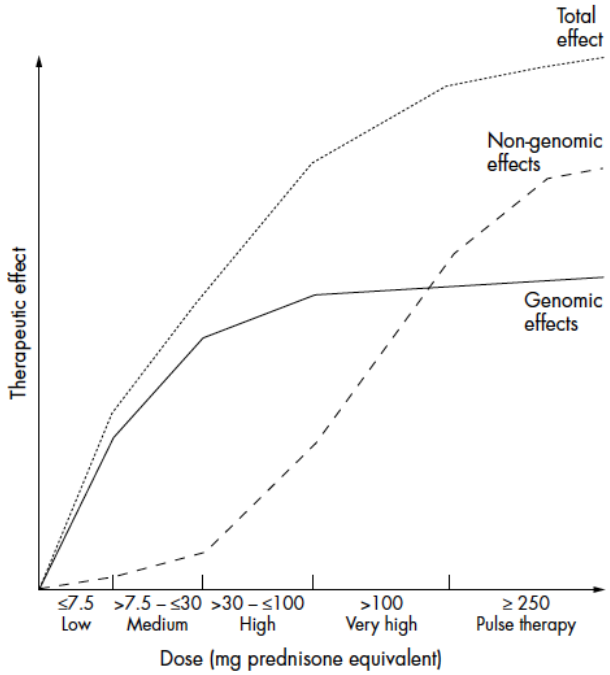

Figure 3.1. Genomic and non-genomic effects on the dose-response relationship of GC

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3.3.3. GC Effects on PMR and GCA

Endothelial cells play an active role in the regulation of inflammation and angiogenesis. The intercellular adhesion molecules on endothelial cells mediate leukocyte trafficking, migration, and development of inflammatory infiltrates [150]. Increased expression of endothelin 1 and endothelin B immunoreactivity has been reported to be in higher concentration in GCA patients compared to controls and may correlate with the degree of systemic inflammation [151]. In another study, Pirro et al. demonstrated that PMR was associated with a significant imbalance between endothelial injury and repair, which was dependent on the degree of systemic inflammation [152]. Levels of C-reactive protein (CRP) were elevated and associated with an increase in circulating endothelial microparticles, of which there was a significant reduction in levels following GC therapy [152].

When triggered by antigens, the immune response starts with activation of macrophages, followed by antigen recognition and activation of T cells. Interleukin-6 (IL-6) is a cytokine that plays an important role in the stimulation of antibody production in the presence of antigens. Two decades ago, the elevation of circulating IL-6 was reported in patients with GCA, and serum levels were reported to correlate with

disease activity [153, 154]. IL-6 functions as an important connector between injured vascular walls and immune cells, and is critically involved in promoting the differentiation of the Th17 lineage, which in turn produces a plethora of cytokines that regulate local and systemic inflammatory effects in GCA [155]. In addition, IL-6 also regulates the induction of anti-inflammatory T regulatory (Treg) cells [155]. Thus, IL-6 has two important roles in GCA – promoting pro-inflammatory T cell immunity and inhibiting the action of opposing anti-inflammatory T cells. In GCA, two distinct cluster of differentiation 4+ (CD4+) T effector cell subtypes have been identified as key regulators: type 17 helper T cell (Th17) and type 1 helper T cells (Th1) [156]. The Th17 pathway has been reported to be very responsive to GC treatment, as GCs rapidly reduce the Th17 effector cytokine production of IL-1, IL-6, IL-17 and IL-23 with simultaneous depletion of both circulating and tissue infiltrative Th17 cells [155, 157]. The rapid decline in these cytokines upon GC initiation is evident by the marked improvement of systemic inflammatory features in patients. Despite the effective reduction of the Th17 pathway, the Th1 cytokine identified in chronic vasculitis in GCA is associated with production of IL-2 and interferon-gamma, and is poorly susceptible to GCs [150]. It is possible that the persistence of Th1 cellular infiltrates despite prolonged GC treatment is responsible for the relapsing nature of GCA [155]. When compared with healthy controls, another study reported that patients with GCA had a decreased frequency of regulatory T cells and Th1, but had a significantly increased percentage of Th17 cells [158]. The initiation of GC treatment reduced the Th1 and Th17 cells, but not the regulatory T cells [158].

Adaptive immune alterations also occurred in PMR patients, mainly represented by the activation of Th17 cells mainly driven by increased IL-6 levels [159]. Patients with PMR have been reported to have higher IL-6, IL-1Ra and serum B-cell activating factor (BAFF) levels that are related with their clinical symptoms [160-162]. GCs act by suppressing IL-6 production rapidly but do not correct the underlying mechanism, resulting in increased IL-6 production following short-term withdrawal of GC, even after several months of treatment [163]. One study also reported that a decrease in the level of circulating IL-6 correlates with remission of clinical symptoms, and that high serum IL-6 receptor levels combined with low haemoglobin values resulted in a ten-fold increased risk of PMR relapse [164]. As with GCA, patients with PMR, when compared to healthy controls, had a decreased frequency of regulatory T cells and Th1, but had a significantly increased percentage of Th17 cells, of which was reduced by GC treatment [158]. In addition, PMR patients have been reported to have a decreased frequency of circulating B cells, of which rapid recovery is seen with the initiation of GC therapy [165].

3.4. Definition of Conventional Terms for Glucocorticoid Doses

In 2001, a panel of experts from the European League Against Rheumatism (EULAR) Standing Committee on International Clinical Studies including Therapeutic Trials gathered to discuss the management of GC therapy in rheumatic diseases [144]. One of the recommendations by the panel was on the relationship between clinical GC dosing and cellular GC actions.

Treatment with prednisolone-equivalent doses of less than 7.5mg per day is termed “low-dose” GC therapy, as this would result in a saturation of GC-receptor complex of approximately 50% [166, 167]. It is often used for maintenance therapy for rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [168, 169], and is associated with relatively few adverse effects, as reported by Da Silva JA et al. The authors did a literature review of the adverse effects of low dose GC in rheumatic disease, which include the following subgroups: musculoskeletal, endocrine, cardiovascular, dermatological, ophthalmological, gastrointestinal, infectious as well as psychological and behavioural disturbances; in addition to an analysis of toxicity data from randomized controlled trials of GC in RA. Of all these adverse effects, they also looked at glucose intolerance and DM, of which the authors concluded that low-dose GC treatment did not increase the risk of DM [170].

“Medium dose” is defined as an administered dose of > 7.5mg, but ≤ 30mg prednisolone equivalent a day with higher receptor saturation ranging above 50% but not completely saturated [166]. These doses are used in initial treatment for primary chronic rheumatic diseases such as acute gouty arthritis, juvenile idiopathic arthritis, PMR and SLE [171]. Adverse effects are considerable and dose dependent, which depends very much on the duration of treatment.

Doses of > 30mg and ≤ 100mg prednisolone equivalent a day are considered as “high dose” because these doses significantly increase receptor saturation in a dose dependent manner resulting in an almost complete receptor saturation of 100% [166]. These doses are usually not administered as long-term therapy because of the occurrence of severe adverse effects, but only used as initial treatments for subacute rheumatic diseases, which includes systemic vasculitides such as GCA [171] and non-life threatening exacerbations of connective tissue diseases such as SLE [172].

Doses of > 100mg prednisolone equivalent a day are considered as “very high dose”. At these doses, the cytosolic receptors are 100% saturated [166], and additional therapeutic benefit of very high doses could be obtained via non-specific, non-genomic effects. This is when physicochemical interactions with cellular membranes occurs and mediated by membrane bound receptor [135-137]. These doses are usually only given as initial doses for life threatening conditions or acute conditions such as vasculitis and SLE [173, 174]. They are not given for long-term treatment because of the severe adverse effects associated with these doses.

The panel of experts also proposed another category, called “pulse therapy”, defined as administration of ≥ 250mg prednisolone equivalent a day, usually given intravenously for less than 5 days. This term refers more to the very high dose given, rather than its intermittent characteristic in terms of time, for the following reasons: the first is that in clinical practice, doses of more than 250mg/day are usually only given as pulse therapy, thus these doses are exclusively given for a few days, but then reduced or stopped directly. Secondly, the non-genomic potencies of GCs generally come into play at these doses, which contributes to the success of very high doses and pulse therapy in acute exacerbations of immunological mediated diseases, such as SLE, vasculitis, RA and polymyositis [173-175]. The panel also suggested that pulse therapy results in termination of disease exacerbations in many cases with a relatively low incidence of adverse effects.

These proposals for nomenclature of GC treatment with its dose-response relationship reflects current and best knowledge available, and more importantly, it also reflects best practice in routine clinical care. Although GCs are widely used because of their immense therapeutic benefits as anti-inflammatory and immunosuppressive agents, many issues remained to be clarified, including their specific mechanism of actions, quantification of adverse events (AEs), as well as measures to counter these AEs associated with long-term GC use.

3.5. Glucocorticoid-Induced Adverse Events (AEs)

Chronic GC therapy is reported to be associated with various AEs, which includes DM, infections, fractures, gastrointestinal bleeding, hypertension, cataract, adrenal suppression, weight gain, myopathy and neuropsychiatric disorder [96, 176]. Despite nearly six decades of established use, the precise risks of these GC-related AEs have been difficult to quantify, mainly because of confounding by indication. Patients with more severe disease often have a greater burden of inflammation, therefore resulting in either a longer duration of treatment, or a higher dose of treatment, which usually leads to a greater risk of developing an AE. Of all the AEs, DM (14%) was ranked as the top most worrisome from a rheumatologists perspective, while it ranked 2nd (7%) (tied with cardiovascular diseases (CVD) (7%)), and after osteoporosis (9%) among patients [15].

Data from the general population in England and Wales showed that at any point in time, approximately 0.9% of the adult population was prescribed oral GCs, with the highest use (2.5%) by those aged between 70 to 79 years old [177]. GCs are relatively inexpensive, but their high usage in medical treatment, ranging from rheumatology to respiratory to endocrine, cancer, bowel diseases and allergies collectively incur significant financial burden to the healthcare system. Manson et al [178] did a cost analysis study, using the incidence rates of seven most commonly reported AEs (fractures, cataracts, DM, peptic ulcer, stroke, myocardial infarction and non-Hodgkin's lymphoma) in the general population of the UK to calculate the estimated total number of events caused by oral GCs. The cost per event or per year of treatment was then applied to estimate the annual economic burden attributable to oral GC-induced adverse events. The authors reported that the total cost for all seven AEs amounted to approximately £165 per oral GC treated patient per year. Diabetes mellitus incurred the second highest cost per patient, amounting to a total of £12.39 cost per treated patient or £2,519.86 cost per episode per year.

3.5.1. Glucocorticoid-Induced Diabetes Mellitus (DM)

Glucocorticoid-induced DM (GC-induced DM) or steroid-induced DM, is defined as an abnormal increase in blood glucose concentration during GC use in patients with or without a previous history of diabetes [16]. The American Diabetes Association's criteria for diagnosing DM is an 8 hour fasting blood glucose of ≥ 7.0 mmol/L, 2 hour post 75g oral glucose tolerance test of ≥ 11.1 mmol/L, HbA1c ≥ 6.5% or a random plasma glucose of ≥ 11.1 mmol/L in patients with symptoms of hyperglycemia [179].

A meta-analysis of studies evaluating the occurrence of DM in non-diabetic individuals treated with GCs reported that the rates of GC-induced DM and GC-induced hyperglycaemia were 18.6% and 32.3%, respectively [180]. A large nested case-control study in the UK using The Health Improvement Network (THIN) primary care database reported an adjusted odds ratio of 1.36 (95% confidence interval (CI): 1.10-1.69) for DM associated with three or more oral GC prescriptions versus no GC use [181]. Another large population-based cohort study using administrative databases in Canada reported that the risk of developing DM among the elderly was significantly higher in those initiated with an oral GC compared to the control group (adjusted rate ratio: 2.31; 95%CI: 2.11-2.54) [182]. Though none of these studies specifically involved PMR or GCA patients, there seemed to be a consensus that use of GCs is associated with an increased risk of developing DM.

The pathophysiology of GC-induced DM is complex and not completely understood, but there have been a few mechanisms proposed pertaining to how GC affects glucose homeostasis in the liver, skeletal muscle, adipose tissues, pancreatic beta cells and small intestines, as shown in Figure 3.2 [183].

Gluconeogenesis is a metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrates such as lactate, glycerol and glucogenic amino acids [184]. The two enzymes involved in the regulation of this pathway are phosphoenylpyruvate carboxykinase (PEPCK) [185] and glucose-6-phosphatase (G6P) [186]. Administration of GCs increase the gluconeogenesis process in the liver, as well as increase glucose production by limiting the metabolic actions of insulin.

In adipose tissues, GCs promote lipid breakdown (i.e. lipolysis), resulting in an accumulation of fatty acids which interfere with glucose uptake [187]. GCs are also reported to increase the plasma concentrations of resistin, an adipose tissue-specific secretory factor and leptin, a hormone released from fat cells in adipose tissues that helps to regulate energy balance; while suppressing adiponectin, resulting in decreased insulin sensitivity and greater insulin resistance.

GCs also interfere with glucose homeostasis in the skeletal muscles by reducing protein synthesis and stimulating protein degradation (i.e. proteolysis), resulting in higher concentrations of amino acids and a reduction in muscle mass or progressive muscle atrophy, otherwise also clinically known as steroid-induced myopathy [188, 189]. GCs also contribute to a reduction in glucose uptake and an increase in the breakdown of glycogen to glucose (i.e. glycogenolysis) [190].

In addition, results from a randomized controlled trial of GC treatment in healthy individuals suggested that GC administration may dose-dependently impair insulin-stimulated capillary recruitment, which is strongly related to insulin resistance, increased postprandial glucose levels and hypertension [191].

Incretins are a group of metabolic hormones that stimulate a decrease in blood glucose levels. The “incretin effect” is the increased stimulation of insulin secretion elicited by oral as compared with intravenous administration of glucose under similar plasma glucose levels. [192]. It is mediated by a gut hormone, glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), a hormone produced by the small intestine that enhances the release of insulin following the intake of food [193-195]. The incretin effect is almost absent in individuals with type 2 DM [196, 197] and diminished in those with impaired glucose tolerance [198] and those who are obese [199]. The use of GCs is associated with a reduction in the incretin effect. It is however, unrelated to the secretion of incretin hormones but is related to insulin resistance and beta cell defects [200].

GCs have also been suggested to inhibit the production and secretion of insulin from pancreatic beta cells [201, 202]. It has been hypothesized that a reduction in both insulin release and biosynthesis [203] and the pro-apoptotic effect of prolonged GC use [204-206] contribute to beta cell failure over time. Another study also reported an increase in fasting and post-prandial glucagon levels after the administration of GCs, which further supports the hypothesis that GCs have a role in inducing beta cell dysfunction [207]. In addition, prolonged use of GCs may elevate the levels of plasma triglyceride and free fatty acids concentrations, leading to lipotoxicity, which indirectly induces beta cell failure [208, 209].

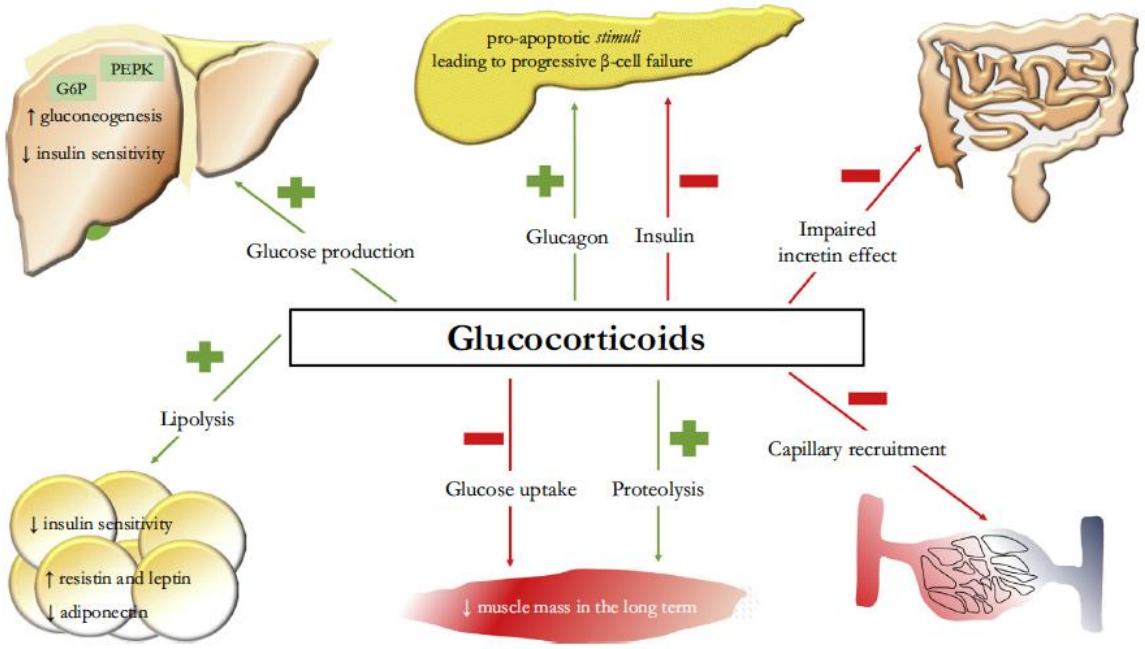


Figure 3.2. Mechanisms of glucocorticoid-induced hyperglycemia in the liver, skeletal muscle, adipose tissue, pancreatic beta cells and small intestine.

Note: Reproduced with permission from RightsLink / Elsevier, permission granted on August 28, 2019 by email. Bonaventura A et al. Steroid-induced hyperglycemia: An underdiagnosed problem or clinical inertia? A narrative review. Diabetes Res Clin Prac. 2018: 139: 203-220

The EULAR task force recently published a paper on defining conditions where long-term GC treatment has an acceptably low level of harm to facilitate implementation of existing recommendations [97]. The authors also outlined a list of studies that were either published within 2010–2015, or were selected older outstanding landmark papers. The results were classified according to the four most worrisome AE of GC therapy as well as general literature on GC-induced AE, which include osteoporosis, DM, CVDs and infections. Since no specific information was given on the studies listed in this report, I conducted a review of relevant papers cited in the report [97] that were related to GC-induced hyperglycemia and/or DM and tabulated the results (Table 3.1) using the PICO (Population, Intervention, Comparator and Outcome) criteria. Effect size and statistical significance of the findings were included if the authors reported them.

Table 3.1: Literature on glucocorticoid-induced hyperglycemia and diabetes mellitus selected by the EULAR task force

1st Author, Year	Population and study design	Treatment Groups (n)	Outcome
Burt, 2012 [210]	Cross-sectional study of subjects with inflammatory rheumatological disease	• Chronic prednisolone for > 6 months (60) • Control: No GC for at least 6 months (58)	• Significantly lower fasting glucose (net difference of 0.3mmol/L) for chronic prednisolone users • Significantly higher post-glucose load glucose concentration (net difference of 1.2mmol/L) for chronic prednisolone users
Den Uyl D, 2012 [211]	Randomized controlled trial (RCT) of patients with early active RA	• Prednisolone 60mg/day (21) • Prednisolone 30mg/day (20)	• Incidence of type 2 DM increased by 17% from baseline ($p<0.01$) (evenly distributed across groups)
Fong, 2013 [212]	Audit of patients commencing high-dose steroid therapy in a tertiary referral hospital	• Prednisolone 25mg/day (49) • Dexamethasone 4mg/day (18) • Hydrocortisone 100mg/day (4) • Combination (9) * minimum of 48 hours	• Mean blood glucose was >/= 8mmol/L in 48% of pts & >/=10mmol/L in 14% of patients • Among those with hyperglycemia, it developed within 48 hours in 94% of subjects

Petersons, 2013 [213]	Matched case control of patients with inflammatory rheumatologic disease	• Subjects initially not on GC, then 7-10 day course of oral prednisolone 6mg/day (9) • Subjects on continuous long-term prednisolone (6.3 +/- 2.2mg/day) (12)	• Prednisolone increased basal endogenous glucose production (EGP*) (p=0.05) & reduced insulin suppression of EGP (p=0.03), peripheral glucose disposal** (p=0.01), first phase (p=0.01) & second phase*** (p=0.02) insulin secretion • Long-term prednisolone users had attenuated insulin suppression of EGP (p=0.03) & non-oxidative glucose disposal (p=0.02), whereas basal EGP, insulin secretion & adipose tissue areas were not significantly different
Raul Ariza-Andraca, 1998 [214]	Matched case control of patients with steroid-induced DM with rheumatic diseases	• Cases (27) • Age & sex matched controls who were also on GC (27)	• Cumulative prednisone dose (26.6 +/- 28g) was associated with the development of steroid-induced DM (OR=6.35, p<0.02) • No significant differences in serum insulin levels
Rostom, 2013 [215]	Matched case control of RA patients	• Cases (120) • Age & sex matched healthy controls (100)	• 6 metabolic syndrome definitions**** were used • Frequency of metabolic syndrome (MetS) was significantly higher than control for all 6 definitions: ranging between 18-48.6% (p<0.05) • GC use was a significant independent predictor of the presence of MetS in RA pts (OR=1.45, CI: 1.12-2.14, p=0.04)
Su, 2013 [216]	Cohort of Taiwanese citizens with and without RA	• RA (4193) • Without RA (596502)	• Relative risk (RR) for T2DM in RA vs. non RA patients a) Men: RR =1.68 (CI: 1.53-1.84) b) Women: RR = 1.46 (CI: 1.39-1.54) • Absolute risk of T2DM in the cohort = 19%
Zeng, 2010 [217]	Cohort of Chinese female patients with SLE	• Patients with SLE on GC: 146	• 46/146 (31.5%) patients had hyperglycemia as defined by the World Health Organization (WHO) diagnostic criteria • Age ≥35 years and high GC doses (defined as current prednisone doses of ≥ 25mg/day or mean monthly prednisone doses of ≥ 570mg/month) were risk factors for hyperglycemia

Note:

** Endogenous glucose production is the formation of glucose from substrates and is a physiological function that normally assists in self-regulation of blood glucose levels*

*** Peripheral glucose disposal is the disposal of glucose from the blood by the peripheral tissues such as skeletal muscles*

**** After a meal, insulin is released within the beta cell, and the first phase of insulin secretion promotes peripheral utilization of the prandial nutrient load, suppresses hepatic glucose production and limits postprandial glucose elevation. This process begins within 2 minutes of nutrient indigestion and continues for 10-15 minutes. The second phase of prandial insulin secretion then follows, and is sustained until normoglycemia is restored.*

*****Joint Consensus 2009, National Cholesterol Education Programme 2004 and 2001, International Diabetes Federation, World Health Organisation and European Group for Study of Insulin Resistance*

The overall trend suggests that GC administration does increase the risk of hyperglycemia, and some cases, GC-induced DM. The results however, must be interpreted with caution for the following reasons. Firstly, most of the studies (especially those with observational designs) were associated with a high risk of bias, especially confounding by indication. The sample sizes for most of the studies were too small to draw any significant conclusions (although in many of the studies, the study authors reported statistically significant results), and in many of the studies, the effect sizes of the study outcomes were not reported. There is also a lot of heterogeneity across studies. The studies include various patient populations (e.g. patients from the European Union, UK, US, Taiwan, China) with various diseases (ranging from children with juvenile idiopathic arthritis to adults with RA) on various treatment regimens (wide range of GC doses and duration depending on indication and disease severity). In addition, the study designs also varied across the literature review – there were a mix of randomized controlled trials, cohorts and case-control designs. There is also a need to update this literature review as the papers selected by the task force was only until 2015, of which there have been an increased interest in the metabolic AEs of GCs in the recent years. It is also worth noting that none of these studies included patients with GCA or PMR, possibly because the diagnoses of GCA and PMR are more challenging, and also because of their lower incidence rate compared to the other rheumatic diseases, therefore there is still a huge research gap in these two disease domains.

As shown in Figure 3.3, the EULAR task force concluded that at doses of ≤5mg/day, there was an acceptably low level of harm; and at >10mg/day, the risk of harm was elevated. At dosages between >5mg/day and ≤10mg/day, uncertainty still exists and patient-specific characteristics need to be taken into consideration to estimate the individual risk of harm. In my opinion, the actual risk of GC-related harm may be hard to define, as there are many factors (such as age and lifestyle) that may influence the risk, even without GC exposure. GCs should still be used for treatment in clinical practice, given the known beneficial effects, but studies with more robust study designs are needed to quantify the risk association with GC use so that existing recommendations on GC therapy may be better implemented and practiced to optimize patient care.

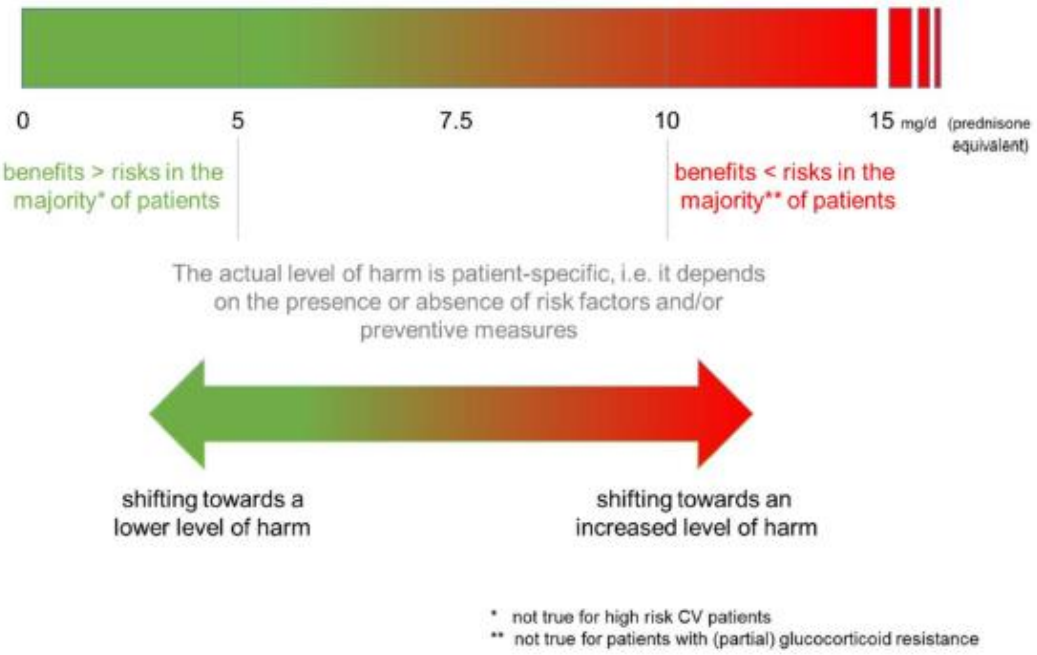


Figure 3.3. The level of harm of long-term GC therapy in rheumatic diseases

Note: Reproduced with permission from RightsLink / BMJ Publishing Group Ltd, permission granted on August 28, 2019 by email. Strehl C et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. Ann Rheum Dis 2016: 75 (6): 952-957

GCs have been used widely in the treatment of PMR and GCA for more than half a century. While their therapeutic efficacy is well established, there is still a huge research gap in terms of determining the magnitude of long-term harm in PMR/GCA. As mentioned in this chapter, DM is one of the most concerning AE associated with GC, and the next chapter will discuss in detail, a systematic review and meta-analysis of the risk of GC-induced DM among PMR and/or GCA patients based on published studies.

CHAPTER 4: ASSOCIATION BETWEEN GLUCOCORTICOID THERAPY AND INCIDENCE OF DIABETES MELLITUS IN POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

4.1. Overview

Long-standing DM is associated with complications such as chronic kidney disease, retinopathy, diabetic neuropathy etc. which often lead to a decline in quality of life (QoL), as well as marked shortening of life expectancy. This is also vital from a health economic perspective as it incurs increased additional healthcare utilization. Despite the importance of this for patients, clinicians and health authorities, there is currently minimal information on the absolute risk of GC-induced DM in patients with PMR and GCA. To address this clinically important question, I conducted a systematic review and meta-analysis of published studies to determine the risk of GC-induced DM in patients with PMR and/or GCA and assessed the potential risk factors associated with the development of DM in these patient groups.

4.2. Methods and Materials

4.2.1. Search Strategy

I searched for published studies or conference abstracts indexed in Pubmed, Ovid (Medline, Embase), Web of Science, Cochrane Library and Cumulative Index of Nursing and Allied Health Literature (CINAHL) from inception of each database to February 2017. The search included terms for patients with PMR and/or GCA who were prescribed oral GC therapy, as well as diabetes-related terms as some individuals eventually developed diabetes. The full search strategy is available in Appendix 1. I also manually screened reference lists of selected retrieved articles to identify further papers that may have been missed in the database search. I made every effort to include all available studies and conference abstracts (regardless of publication year), which included contacting the first authors by email if necessary. The selection process of identifying relevant studies is shown in Figure 4.1.

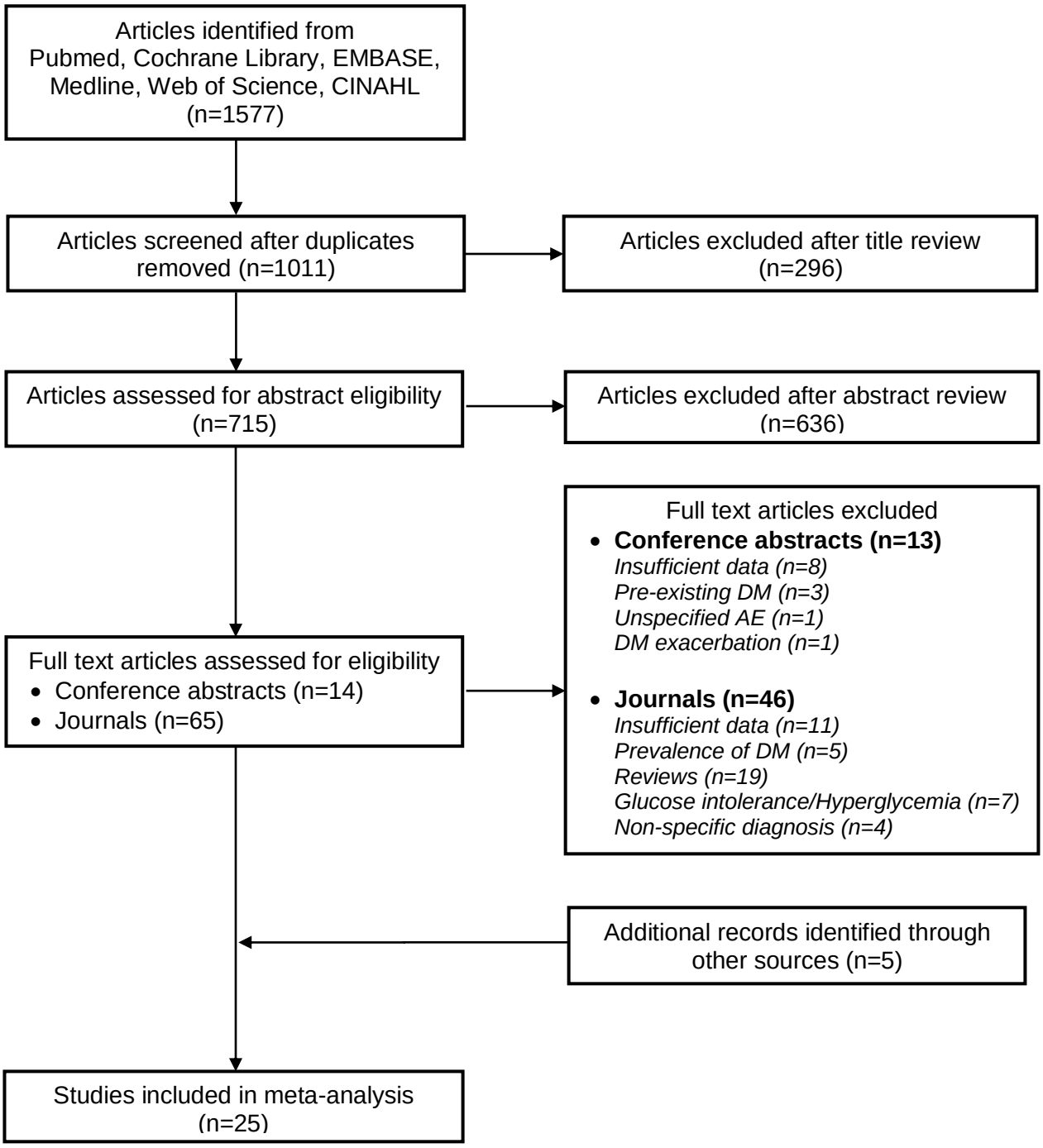


Figure 4.1: Flowchart of the selection process of studies

4.2.2. Eligibility Criteria

4.2.2.1. Inclusion Criteria

- All original research articles and conference abstracts that reported new onset diabetes following exposure to oral GC therapy in patients with PMR and/or GCA
- All randomized controlled trials (RCTs), cohort studies, cross-sectional studies and nested case-control studies

4.2.2.2. Exclusion Criteria

- All original research articles and conference abstracts that reported any pre-existing diabetes or any pre-diabetic states (e.g. increased fasting glucose, glucose intolerance) or exacerbation of pre-existing diabetes (e.g. worsened diabetes, addition of insulin)
- Case series and case reports

4.2.3. Study Selection

A colleague and I independently carried out the initial screening of search results by title and abstract, using the abstract screener software “Abstrackr” [218] and Endnote X7.4 (1988-2015 Thomson Reuters). Study eligibility was determined independently and any disagreements were resolved by consensus with my supervisor.

4.2.4. Data Extraction

Data were extracted independently by my colleague and I using a standardized data collection Microsoft Access database. Any discrepancies in data extraction were resolved by consensus. For articles containing more than one study treatment group, I included the “GC-only” arm and excluded the groups where there was another study drug in addition to GCs. Information extracted included journal information, publication year, year/s of enrollment, study design, patient demographics (age, sex, body mass index (BMI), weight, height, medical history, family history, glucose level and hemoglobin A1C (HbA1c)), number of patients recruited, number of patients with DM, definition of DM, GC indication, treatment dose and duration, and duration of follow-up. Patient populations were classified as “PMR” or “GCA” based on their primary diagnosis as determined by the authors. Non-English articles were translated with the help of Google Translate and colleagues who were native speakers of the respective languages.

4.2.5. Assessment for the Risk of Bias

I used the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [219] as a checklist (Appendix 2) to ensure proper evaluation of quality and completeness of the observational studies.

The risk of bias was also assessed, using the Cochrane Collaboration's tools proposed by the Cochrane Group for RCTs [220] and for cohort studies [221]. My colleague and I did the risk of bias assessment independently, and discrepancies were resolved by consensus.

Table 4.1: The Cochrane collaboration's tool for assessing risk of bias in RCTs [220]

Domain	Support for judgment
SELECTION BIAS Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
PERFORMANCE BIAS Blinding of participants and personnel	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
DETECTION BIAS Blinding of outcome	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
ATTRITION BIAS Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
REPORTING BIAS Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.

Table 4.2: The Cochrane tool for assessing risk of bias in cohort study [221]

Domain	***Support for judgment***
Selection of population	Was selection of exposed and non-exposed cohorts drawn from the same population, presenting at same points of care over the same time frame?
Assessment of exposure	Can we be confident in the assessment of exposure? Was the exposure retrieved from secure records (e.g. surgical records, pharmacy records) or was it based on self-reporting or interviews?
Ascertainment of outcome not present at start of study	Can we be confident that the outcome of interest was not present at start of study?
Adjustment of prognostic variables	Did the study match exposed and unexposed for all variables that are associated with outcome of interest or did the statistical analysis adjust for these prognostic variables?
Assessment of prognostic variables	Can we be confident in the assessment of the presence or absence of prognostic factors? How was the prognostic data extracted? Was it based on review of charts and established databases with reproducibility demonstrated?
Assessment of outcome	Can we be confident in the assessment of outcome? Was it based on record linkage and documented medical records? How was the outcome of interest defined?
Assessment of Follow-up	Was the follow up of cohorts adequate? Were there any missing outcome data?

I used Cohen's kappa score to test for interrater reliability, where 0 represents the amount of agreement that can be expected from random chance, and 1 represents perfect agreement between the raters [222]. There were two different sets of Kappa scores – one for all RCTs, and the other for all observational studies. Kappa result can be interpreted as follows [222]:

- 0.00-0.20: None
- 0.21-0.39: Minimal
- 0.40-0.59: Weak
- 0.60-0.79: Moderate
- 0.80-0.90: Strong
- > 0.90: Almost perfect

4.2.6. Statistical Analysis

Baseline characteristics such as age and sex were summarised using descriptive statistics. The weighted mean and standard deviation were calculated by taking into account the sample size of each study for the following variables: age at baseline, proportion of females, cumulative dose, duration of GC use and duration of follow-up. I chose to use the weighted mean as this method takes into consideration the relative importance (based on sample size) of each study. The incidence proportion of new DM cases was modeled using binomial regression where the outcome variable was the number of newly diagnosed DM patients divided by the number of GC-treated patients at risk of developing DM. The candidate explanatory variables included were: mean age, year of enrolment, diagnosis (PMR or GCA), cumulative dose and treatment duration. Variables were selected a-priori based on clinical knowledge for inclusion in the multivariable modelling rather than taking a purely data-driven approach. Results were presented as odds ratio (OR) and 95% confidence interval (CI). I carried out a meta-analysis using a random effects model, of which it is assumed that the observed estimates of effect can vary across studies because of real differences in the effect for each study, as well as sampling variability. Heterogeneity in the effect may be caused by differences in study population (e.g. age), interventions received (e.g. dose of GCs), and follow-up duration [223].

Heterogeneity was assessed using the I-square and tau statistics. I-square values less than 40% suggest that heterogeneity might not be important; values within the range of 30-60% suggest that there is moderate heterogeneity, while values above 75% represent considerable heterogeneity [224]. Statistical analysis was done with R (Version 3.3.1.) [225].

4.3. Results

Table 4.3: Studies included in the meta-analysis

First Author, Publication Year	Country	Population	Study Design	Study Enrolment period
Von Knorring, 1979 [226]	Finland	PMR	Cohort	1967-1977
Godeau, 1982 [227]	France	GCA	Cohort	1966-1979
Chuang, 1982 [47]	USA	PMR	Cohort	1970-1979
Behn, 1983 [228]	UK	PMR	Cohort	1968-1980
Gouet, 1985 [229]	France	GCA	Cohort	1970-1984
Andersson, 1986 [230]	Sweden	GCA	Cohort	1968-1975
Delecoeuillerie, 1988 [231]	France	GCA	Cohort	1976-1986
Nesher, 1994 [232]	Israel	GCA	Cohort	1978-1992
Gabriel, 1997 [176]	USA	PMR	Cohort	1970-1991
Jover, 2001 [14]	Spain	GCA	RCT	1993-1997
Proven, 2003 [13]	USA	GCA	Cohort	1950-1991
Hutchings, 2007 [233]	UK	PMR	Cohort	2001-2003
Salvarani, 2007 [234]	Italy	PMR	RCT	2003
Cimmino, 2008 [235]	Italy	PMR	RCT	1998
Schmidt, 2008 [236]	Germany	GCA	Cohort	1997-2006
Dasgupta, 2009 [237]*	UK	PMR	Cohort	2001
Khalifa, 2009 [238]	Tunisia	GCA	Cohort	1986-2003
Martinez-Lado, 2011 [239]	Spain	GCA	Cohort	1992-2006
Mazzantini, 2012 [240]	Italy	PMR	Cohort	1997-2009
Dunstan, 2014 [79]	Australia	GCA	Cohort	1991-2011
Alba, 2014 [241]	Spain	GCA	Cohort	1995-2007
Seror, 2014 [242]	France	GCA	RCT	2006-2010
Muller, 2016 [243]	France	GCA	Cohort	2002-2008
Carbonella, 2016 [244]	Italy	GCA	Cohort	NA
Faurschou, 2017[245]	Denmark	GCA	Cohort	1997-2015

RCT=Randomized controlled trial
PMR=Polymyalgia rheumatica
GCA=Giant cell arteritis
* Conference abstract

My systematic literature search identified 25 eligible publications consisting of 24 journal articles and 1 conference abstract. Of the final 25 studies, 21 were cohort studies and four were RCTs. Nine studies reported on predominantly-PMR patients while 16 studies reported predominantly-GCA patients. Nine of the 16 studies I classified as GCA studies included some patients with polymyalgic symptoms (range 37.3%-62.3% of patients). Four of the nine studies I classified as PMR studies including some patients who also had been diagnosed with GCA (range 13.0%-26.7% of patients), but I decided to classify them as PMR studies because that was the primary diagnosis as determined by the authors.

Most of the studies were conducted in Europe (n=20), followed by USA (n=3), Australia (n=1) and Tunisia (n=1). A total of 19 studies started enrolment before the year 2000, the earliest commencing study enrolment in 1950. Details of the individual studies are shown in Table 4.1.

Table 4.4: Summary characteristics of individuals with PMR and/or GCA

	Total (n=3743)	**PMR (n=920)**	**GCA (n=2823)**
Demographics			
Age at baseline*, years	74.1 (3.6)	71.6 (3.1)	74.9 (3.7)
% Female	67.8 (10.6)	71.0 (10.7)	66.7 (10.5)
Glucocorticoids use **			
Cumulative dose, g	7.6 (4.2)	5.6 (3.3)	8.2 (4.5)
Duration of GC use, years	2.4 (1.5)	2.1 (1.2)	2.5 (1.6)
Follow-up			
Duration, years	5.9 (4.1)	4.4 (3.3)	6.4 (4.4)

All data are presented as a weighted mean (standard deviation) across studies
**Age at diagnosis (n=11), age at study inclusion (n=3), age unspecified in study (n=11)*
***Doses are shown as oral prednisolone equivalent*

The weighted mean age across the studies reviewed was 71.6 years for PMR and 74.9 years for GCA, with approximately two-thirds being female. Cumulative dose in the GCA group was higher than the PMR group, with longer treatment duration and follow-up as well (Table 4.2).

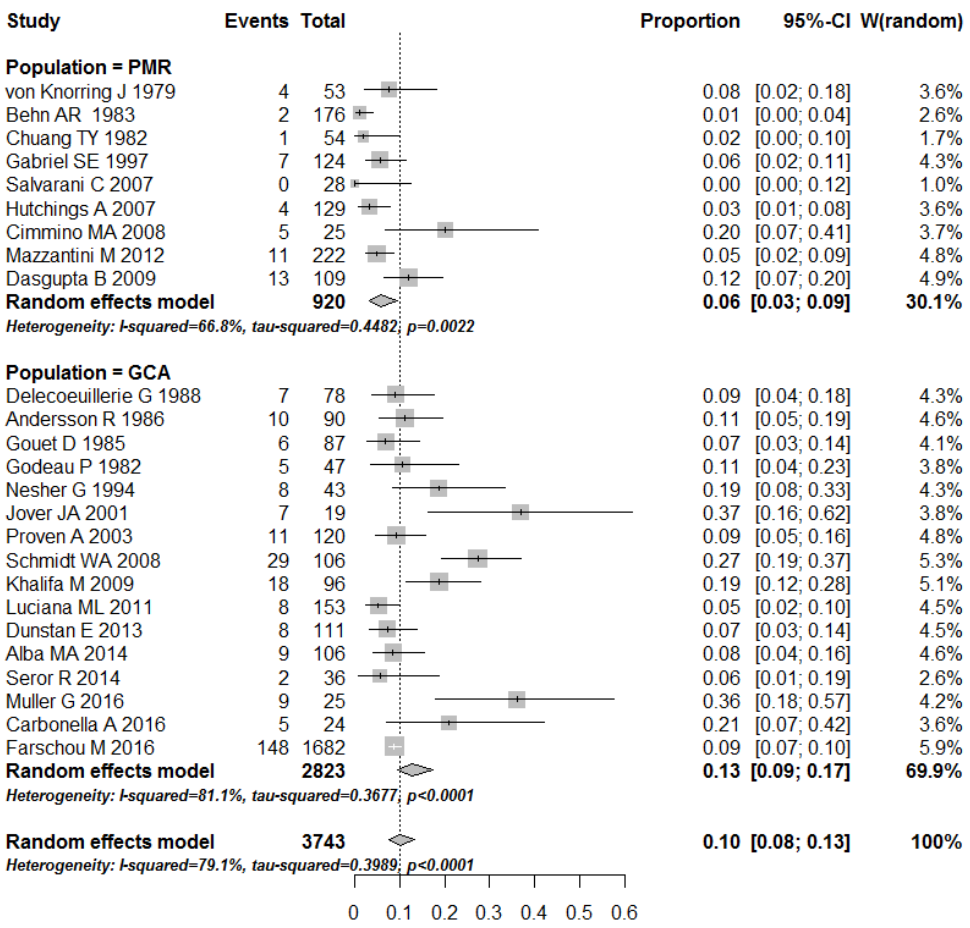


Figure 4.2: Proportion of PMR and GCA patients who developed new-onset DM with 95% confidence intervals

Note: The W (random) shows the percentage weights of individual studies in the random effects model

The incidence proportion of patients with PMR who developed new-onset DM was 6% (95% CI: 3%-9%) and the incidence proportion of patients with GCA who developed new-onset DM was 13% (95% CI: 9-17%) (Figure 4.2). Of all the newly diagnosed DM reported, 7 occurred during follow-up and 18 were unspecified.

Table 4.5: Results from final multivariable model predicting risk of GC-induced DM

Covariates	OR	95% CI	*p-value*
Mean age (years)	0.97	(0.89, 1.04)	0.3010
Year of enrolment	1.01	(0.99, 1.04)	0.1405
Cumulative dose (g)	1.03	(0.89, 1.16)	0.6723
Duration of GC use (years)	1.17	(0.98, 1.41)	0.0948
Diagnosis			
PMR (Reference group)	1		
GCA	2.37	(1.64, 3.52)	<0.001

Note: Adjusted for mean age, year of enrolment, cumulative dose, duration of GC and diagnosis of PMR or GCA

In my study, the risk of developing new-onset DM among GCA patients doubled compared to PMR patients, which is consistent with the results of the meta-regression (13% vs. 6% respectively). All other variables, including mean age, year of study enrolment, cumulative GC dose and duration of GC use were not statistically significant.

My attempt to identify predictors of DM in this meta-analysis is more exploratory in nature as there are some limitations in the multivariable modelling. With this limited dataset and large number of potential explanatory variables, there is a risk of overfitting and may limit generalisability of this model. Other limitations of the model include the assumption that there is a linear relationship between variables, but it is also possible that collinearity may exist among some of the predictor variables. I excluded follow-up duration in my analysis because there is a high possibility that follow-up duration was confounded with diagnosis since GCA patients were more likely to receive higher GC doses and for longer duration, thus tend to be monitored over a longer period of time.

Table 4.6: Risk of bias of randomized controlled trials

	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)
Jover JA et al, 2001	L	U	L	U	L	L
Salvarani C et al, 2007	L	L	L	L	L	U
Cimmino MA et al, 2008	L	U	L	L	L	U
Seror R et al, 2014	L	L	L	L	H	U

L	*Low risk of bias*
H	*High risk of bias*
U	*Unclear risk of bias*

Most RCT studies scored low risk in most domains. In some cases, however, we were unable to assess the risk of bias due to insufficient information (Table 4.4).

Table 4.7: Risk of bias of observational studies

	Similar population	Assessment of exposure	Outcome not present at start of study	Adjustment of prognostic variables	Assessment of prognostic variables	Assessment of outcome	Adequate follow-up
Von Knorring J et al	++	+	-	--	--	-	+
Chuang TY et al	+	++	--	--	++	--	+
Godeau P et al	-	-	--	--	--	--	--
Behn AR et al	++	++	--	--	--	--	+
Gouet D et al	+	+	--	--	--	--	+
Andersson R et al	++	++	--	--	--	--	+
Delecoeuillerie G et al	++	++	--	--	--	--	+
Nesher G et al	++	++	--	-	+	--	+
Gabriel SE et al	++	++	+	+	++	++	+
Proven A et al	++	++	+	+	++	++	+
Hutchings A et al	++	++	--	+	+	+	--
Schmidt WA et al	++	++	-	+	+	--	-
Dasgupta B et al	+	-	-	--	--	--	+
Khalifa M et al	+	+	--	--	--	--	--
Martinez Lado L et al	+	++	--	+	++	--	+
Mazzantini M et al	++	++	++	+	+	++	+
Dunstan E et al	++	++	+	++	+	--	+
Alba MA et al	++	++	+	++	--	+	+
Carbonella A et al	+	--	--	--	--	--	-
Farschou M et al	++	++	+	-	++	++	++
Muller G et al	++	+	--	--	+	--	-

++	*Definitely yes (Low risk of bias)*
+	*Probably yes*
-	*Probably no*
--	*Definitely no (High risk of bias)*

The overall risk of bias was high for many of the observational studies, especially for domains relating to the outcome and prognostic variables (Table 4.5). DM was not precisely defined in the studies and there was a lack of uniformity on how it was measured. Of the 25 studies, only six included an a-priori definition of DM. Even with these six studies, various measurement methods were used, ranging from random blood sugar estimations to fasting plasma glucose levels to use of pharmacological interventions such as oral anti-diabetic drugs and insulin. In 13 articles (52%), adjustment and assessment of prognostic variables were not well accounted for. The Kappa score for RCTs was 0.779, and 0.804 for observational studies. Approximately 56% of the disagreements for observational studies were between pairs of (1) “probably yes” and “yes” or (2) “probably no” and “no”. When combined the “probably yes” and “yes” as one criterion, and “probably no” and “no” as another criterion, the Kappa score was increased to 0.871.

4.4. Discussion

There is overwhelming epidemiological and pathophysiological evidence that GC therapy may cause DM [246-250]. My aim was to estimate the effect size in this particular population for the purpose of informing clinical decisions about care of patients with PMR and/or GCA and health economic analyses about the cost-effectiveness of new therapies for PMR and/or GCA. In my meta-analysis of published literature, the estimated incidence proportion (cumulative incidence) of new-onset diabetes was 6% (95%CI: 3%-9%) for patients with PMR and 13% (95%CI: 9%-17%) for patients with GCA. These figures are plausible: they are slightly higher than current UK population rates for patients of this age and sex, of which the expected background incidence rate of DM over 4.4 years in PMR patients and 6.4 years in GCA patients (follow-up duration) has been reported to be 4.8% and 7.0%, respectively [251]. It should however, be interpreted with caution as the incidence proportion was reported in my study, and not the incidence rate. Therefore it would be difficult to compare to estimates from other studies, as the person-years at risk was not accounted for in my study. It should be noted that many of the studies I reviewed were conducted at a time when population incidence of DM was lower than it is now [251]. In addition, a few studies [252-256], including a recent meta-analysis [257] have shown that GCA

patients had a lower prevalence of DM at the time of GCA diagnosis compared to age- and sex-matched controls, which may suggest that the magnitude of GC-induced DM to be greater than expected. Two cohort studies, using Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN) data [258, 259] found no difference in pre-existing DM between GCA patients and their age and sex matched comparators, while another 2 studies [260, 261] reported a higher prevalence of DM in the GCA cohort as compared to their age and sex matched comparators. Heterogeneity in study design was high. The study populations were diverse in terms of disease manifestation, situated at different geographical locations, and were also subjected to different treatment strategies. In addition, the studies included in this meta-analysis were done over a span of 40 years, during which clinical practice is likely to have changed. This heterogeneity was also reflected in high statistical heterogeneity identified by our meta-analysis as assessed by the I-squared and tau statistics. One particular difficulty was the lack of clarity and consistency regarding the definition of DM in the studies identified. It was also difficult to identify the onset of DM, as most studies (72%) did not specify the timing of DM occurrence during follow-up.

Since most of the studies reviewed did not have the primary aim of quantifying DM risk in PMR and/or GCA, the detail available in published reports was limited. For example, summary measures such as mean starting dose, mean treatment duration and mean cumulative dose cannot fully capture the pattern of GC dosing used for PMR and/or GCA, where the highest GC burden occurs during the initial stages of treatment [21, 7, 262]. A very recent Danish study [245] reported that the incidence risk ratio of new-onset DM was 7.0 (95% CI: 5.2-9.3) in the GCA cohort during the first year of observation when compared to the general population. Beyond the first year, they reported that the incidence rates for DM were not significantly increased. In another large observational study of 5,011 GCA patients, the incidence risk ratios of DM was 1.4 (95% CI:1.2-1.7) as compared to matched non-GCA patients [263]. The median time for the occurrence of DM in the GCA group was 1 year, which supports the hypothesis that the risk of developing GC-induced DM may be highest within the first year of GC use. Other studies emphasized cumulative dose: a very recently published US study reported that the risk for new-onset DM rose by 5% with each 1000mg of GC exposure (in prednisolone-equivalent dose (PED)) in GCA patients [264]. It was difficult to explore these factors further in the meta-analysis due to limited information and heterogeneity in population, geographical location and treatment practices. The addition of my PhD project to the meta-analysis may help provide a better estimation of DM risk as it has a large sample size and designed with the primary aim of quantifying DM risk associated with GC use in PMR and/or GCA patients.

Because GCs are the mainstay of treatment for PMR and GCA, it was not possible to disentangle the effect of the disease from the effect of the treatment. It is however known that systemic inflammation itself can also induce a state of insulin resistance [265, 97] so it is plausible that the inflammatory disease itself (PMR or GCA) could have contributed to the risk of new-onset DM. In addition, some medications commonly prescribed to elderly patients may contribute to the risk of DM (e.g. thiazide diuretics, beta-blockers, niacins and statins). These were not reported by the studies identified, as their primary focus was not on DM.

Confounding by indication could not be excluded. For example for the observational studies, clinicians may have been less willing to prescribe higher GC doses to control disease activity in obese patients at high risk of DM.

The overall risk of bias was high for many of the observational studies, especially for domains relating to the outcome and prognostic variables. Therefore, results should be interpreted with caution. One of the potential next steps is to carry out a sensitivity analysis that includes only selected studies with a low risk of bias and determine if the results differ from the main analysis.

4.5. Conclusion

Findings from this study underline the importance of screening for GC-induced DM in patients with PMR and/or GCA in clinical practice [21, 7] and can also help inform dietary and lifestyle advice in patients commencing GC for PMR and/or GCA. As well as limitations inherent to the meta-analysis itself, there remains considerable uncertainty in our estimate of the absolute risk of DM in PMR and/or GCA, since most published studies were not conducted with this as the primary aim. Furthermore, there is virtually no direct evidence as to which patients are at the greatest risk of DM, which would inform decisions as to how treatment should be individualized. To address this issue, I will be discussing in detail the main focus of my PhD project in the next chapter, which is to quantify the incidence of type 2 DM associated with GC use in patients diagnosed with PMR and/or GCA using CPRD data.

CHAPTER 5: METHODS

5.1. Overview

This chapter seeks to tackle the aims set out in chapter one through the use of Clinical Practice Research Datalink (CPRD). There were three aims in this study. Firstly, to quantify diabetes mellitus (DM) risk associated with oral glucocorticoid (GC) use in primary care within the initial two years of polymyalgia rheumatica (PMR) and/or giant cell artertis (GCA) diagnosis. Secondly, to assess the prescribing pattern of oral GC use in patients with PMR and/or GCA in a primary care setting; and thirdly, to compare CPRD-derived data with data I extracted from primary care prescription data collected directly from registered primary care general practitioners (GPs). The first two chapters provide the basis on why it is crucial to quantify the risk of DM associated with oral GC use in patients with PMR and/or GCA. Patients with PMR and/or GCA are not only often prescribed with high GC doses, but also for a considerably long duration compared to other GC-treated diseases like asthma. Chapter three describes how GCs are like a double-edged sword – while GCs ameliorate symptoms, they also induce toxicities such as DM. Oral GCs are almost exclusively prescribed in PMR and/or GCA; therefore these patients are considered to be high risk of developing toxicities over time. Chapter three also describes in detail the pharmacokinetics and pharmacodynamics of GCs, including the relationship between dosing regimens and therapeutic or detrimental effects. Chapter four provides an estimate of the risk of DM in PMR and/or GCA patients based on published literature. This chapter also provides the rationale for the importance of using large electronic health records data such as CPRD to provide a better estimate of DM risk associated with GC use. The current chapter (chapter 5) will include a section on ethical considerations, followed by a brief discussion on the different data sources, which includes how data were collected and linked to provide the dataset from which the study population was derived from. The identification of study population and outcomes will also be discussed. Final sections will outline key steps in data preparation and the statistical analyses.

5.2. Ethical Considerations

5.2.1. Ethical Approval

CPRD is a UK government research service supported by both the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR) to promote healthcare research through the use of electronic health records. All CPRD-related studies have to be approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research, of which the following aspects are of priority: a well-defined hypothesis; clear application of methodology, including consideration of possible bias and confounding; as well as compliance with all requirements to ensure patient confidentiality. All electronic patient records had been anonymized, therefore no patient identifiable data were available in the dataset other than the month and year of birth. Ethical approval for this study had been as part of my supervisor's (Dr Mar Pujades-Rodriguez) project approval (Approval number: 16_146; included as Appendix 3).

5.2.2. Legal Framework

In addition to ethical approval, to comply with the General Data Protection Regulation (GDPR) and ensure that participants' confidentiality and privacy were well protected, the linked CPRD database is stored securely on a university password protected drive, and has restricted access to named researchers. One of the practical steps I did was to familiarize myself with the relevant legal and ethical requirements before I started working on the dataset. I completed multiple ethics-related modules (e.g. Good Research Practice, Good Clinical Practice on Secondary Care, Research Data and Confidentiality and Ethics Reviewers Training) to ensure that I fully understood the guidelines and standards. I took appropriate steps to work within these frameworks (e.g. only publish data which is non-patient identifiable) to ensure data security and protect patient confidentiality.

5.3. Data Sources

5.3.1. Clinical Practice Research Datalink (CPRD)

Approximately 98% of the UK population is registered with a primary care general practitioner (GP) [266], who acts as the first point of contact for patients for any health-related issues. Patients may then be referred to other services such as hospital care as necessary. At each visit, patient data are routinely recorded electronically, and if they are registered with a CPRD-participating practice, then the information will be uploaded to the CPRD secure servers on a monthly basis unless the patients request to opt out of data sharing at their respective GPs. CPRD is one of the largest ongoing longitudinal databases with approximately 11.3 million patients (reported in 2013) from over 600 general practices across England, Wales, Scotland and Northern Ireland. This database mainly consisted of GPs from England, of which London had the highest number of patients (13.6%), followed by the North West region (11.1%), and the South East Coast (10.0%) [9]. Approximately 75% of English practices (as of 2013) were part of the CPRD linkage scheme and provided patient-level information. Patient-level data were then linked to other data sources such as Hospital Episode Statistics (HES) [267] and Office of National Statistics (ONS) mortality registry [268] and Index of Multiple Deprivation (IMD) [269].

Information recorded includes demographics, medical diagnoses, signs and symptoms, drug prescriptions, referrals, clinical and laboratory investigations and administrative dates (e.g. registration, de-registration and death). Read codes, a coded thesaurus of clinical terms used by the National Health Services (NHS) during the study period, were used to classify medical information, while product codes (based on the British National Formulary (BNF)) are assigned to prescribed medications [270]. In addition to these codes, there are also GP-uncoded notes, often entered as free text. These free texts are not available to researchers as they often contain identifiable information. Validation studies have reported a high positive predictive value of reported diagnoses and prescriptions in this database [271, 272].

The strengths of CPRD data include the following: It is one of the largest routinely collected health data that spanned primary care practices across UK and linked to the mortality registry, with a relatively long follow-up duration (median follow-up of 9.4 years for active patients and 5.1 years for the overall CPRD population)[9]. It is also reported to be broadly representative of the UK population in terms of age, sex and ethnicity [9].

CPRD is however, not without limitations. One of the key limitations is missing data - Information may be missing because it is not compulsory to have it recorded. For example, blood pressure is not routinely measured at every GP visit, unless there is an indication that it needs to be measured. Another limitation of CPRD is the incompleteness or delayed recording of information from secondary care as this information need to be manually entered into patient record. The variability in completeness of data across patients and across time would therefore require careful consideration to ensure that the study is not biased due to these limitations.

5.3.2. Hospital Episode Statistics (HES) [267]

Hospital Episode Statistics (HES) is a data warehouse for all inpatient admissions for NHS funded patients, which goes as far back as 1989. Clinical information about diagnoses has been linked to CPRD, of which data have been collated centrally and coded by administrators. Diagnostic data recorded in HES are coded using the International Classification of Diseases (ICD)-10 coding classification.

5.3.3. Death Registration Data by Office for National Statistics (ONS) [273]

The Office for National Statistics (ONS) mortality data contains information related to a person's death obtained from the death certificate for all deaths registered in England and Wales. It includes information on the underlying cause of death and date of death using ICD-9 (for information prior to 2000) and ICD-10 codes (for information after 2000).

5.3.4. Index of Multiple Deprivation (IMD) [274]

The IMD is a measure of relative deprivation for neighborhoods in England. It is used to compare small areas across England, identify the most deprived areas and explore the various domains of deprivation. The seven domains of deprivation are: income deprivation, employment deprivation, education, skills and training deprivation, health and disability, crime, barriers to housing and services, as well as living environment deprivation [275]. The small area data provided by CPRD is at the lower layer super output areas (LSOA) level which are typically built from 4-6 output areas with an average of 1,600 residents [276]. The relative deprivation of a particular area in England is determined by ranking each area from most deprived to least deprived. The IMD variable in CPRD has been divided into 20 groups to prevent disclosure of patient

location. The raw data of LSOA used to be made available to researchers in the past, but it is no longer available.

5.4. Data Linkage [273, 277]

NHS Digital is a trusted third party with the responsibility and authority to link identifiable data between CPRD, HES and ONS across England. Linkage is crucial to provide a more comprehensive and complete set of data needed for quality research. Linking ONS and CPRD creates a richer dataset that captures the date and the underlying cause of death of patients registered in the practices. The IMD is linked to CPRD data through the patient postcode, which serves as a useful proxy for socio-economic status.

5.5. Study Population

There are three levels of population hierarchy [278]. First, there is the “source population”, which comprises all individuals who are registered in a GP practice in the UK. A subset of this population is the “database population”, comprising all individuals included in the CPRD database. The smallest subset is called the “study population”, of which individuals are selected from within the CPRD database using codes and algorithms based on the specific inclusion and exclusion criteria of the study. For the purpose of this PhD project, the term “study population” will subsequently be used.

Patient records for my study population were extracted from the CPRD database based on standardized diagnostic codes (Read codes); and for drug exposure, the BNF drug product or substance codes were used. Based on these diagnostic and prescription codes, relevant electronic health records were obtained. The data were then extracted as a number of separate data files, of which the information was linked to individual patients via a unique patient identifier – the patient ID. The unique patient ID is present in all files extracted and allows all the information to be linked to one specific patient. Table 5.1 provides details of the CPRD data files used in this project.

Table 5.1: Description of CPRD data files obtained

File Type	Data Description
Cohort	Demographic data including date of birth, gender, IMD, registration date
Clinical (1)	Clinical diagnosis of PMR and/or GCA, including diagnostic codes and dates
Clinical (2)	Clinical diagnoses of diabetes, including different types of DM codes and dates
Prescription (1)	GC drug prescriptions, including drug code, dates, strength, formulation
Additional	Contains information on smoking status and body mass index (BMI)

A clear set of pre-defined inclusion and exclusion criteria were then applied to identify the study population and the start of follow-up for each patient.

5.5.1. Inclusion Criteria

All patients who had:

- A first ever diagnosis of “polymyalgia rheumatica”, “giant cell arteritis”, “temporal arteritis” or “horton’s disease” recorded in CPRD or HES between 1st January 1998 and 30th September 2015. I chose to only look at incident cases; therefore only patients with a first occurrence of PMR and/or GCA were included
- At least twelve months of CPRD-defined up-to-standard (UTS) data available prior to the start of follow-up to rule out any prior diagnosis of PMR or GCA (the “up-to-standard” date is a practice-based quality metric based on the continuity of recording and number of recorded deaths. The UTS date is calculated for each participating practice, corresponding to the latest data at which practices meet these minimum quality criteria. [9])
- At least one oral GC prescription during the duration of study follow-up

5.5.2. Exclusion Criteria

- Patients with pre-existing PMR and/or GCA (i.e. prevalent disease)
- Patients with a diagnosis of DM in CPRD or HES recorded before their PMR or GCA diagnosis
- Patients without any oral GC prescription during the duration of study follow-up
- Less than one year of up-to-standard registration in CPRD
- Under 18 years of age at the date of the first recorded PMR/GCA diagnosis
- Not eligible for data linkage due to one or more of the following reasons:

- Registered at the practice after the transfer of encrypted unique patient identifiers from NHS digital to the end-user
- No valid identifier for linkage (either NHS number or postcode)
- Opted out or dissented from CPRD or the linkage scheme

5.5.3. Definition of Start and End of Study Follow-up

The study entry date was created, defined as the latest date of the following:

- 1st of January 1998
- Date of first recorded diagnosis of PMR and/or GCA
- UTS date plus one year
- Date of GP practice registration plus one year.
- At least 18 years of age

The end of follow-up date was determined, defined as the earliest of the following dates:

- End of data collection (date of last collection date for the practice or date of transfer of the patient out of the practice)
- Death or
- DM diagnosis

The date of death was identified from the primary care data CPRD or linked ONS mortality data, where available. For patients who had a recorded death in both CPRD and ONS, the date of death from ONS was selected as they were taken from the death certificate for all registered death.

For the majority of my analyses pertaining to DM risk and oral GC exposure, I looked at the initial two years of follow-up following diagnosis of PMR and/or GCA. When studying the overall GC prescribing pattern in primary care however, I looked at the starting dose, daily dose, cumulative dose and treatment duration relating to overall follow-up duration, and comparing the results from my study to other published literature.

5.5.4. Factors of Interest

5.5.4.1. Exposure

The main exposure for this PhD project was prescribed oral GC dose in primary care, and the first step was to prepare and clean the prescription data. There were 2 sets of prescription data – one being the CPRD derived data managed by the CPRD team; and the other being data that I extracted from primary care data collected directly from registered primary care GPs and linked to CPRD. This is preliminary work to compare the information derived from CPRD with my extracted data to assess the quality and completeness of CPRD derived data, which is often used by researchers in the analyses performed in many publications. All subsequent analyses were done using my extracted variables, by applying rules described in other studies and that others have also used in the past [12, 279]. These rules are detailed at the end of this section (pages 63 and 64).

The prescription database contains information on GCs in various dosage forms, which has been categorized based on their route of administration: oral, intramuscular (IM), intra-articular (IA), rectal, topical, inhaled, and nasal. For the purpose of this PhD project, I decided to only include oral prescriptions, as intravenous GC prescriptions are almost never prescribed by GPs for these diseases.

Information pertaining to the dose, frequency and duration of each oral GC prescription was then extracted from the following variables:

- “Product name” – This variable documents the names of all GCs prescribed in primary care
- “Quantity prescribed” – This variable documents the quantity of oral GC prescribed for each visit
- “Dosage instructions” – This variable contains free text as documented by GPs in primary care. Most of the information relating to dose and frequency were extracted from this variable
- “Duration of treatment” – This variable documents the duration of GC treatment prescribed

The various types of oral GCs with different anti-inflammatory potencies in the prescription database were identified from the product name, and the potencies of these prescribed GCs were standardized according to the most commonly used GC, prednisolone, to obtain the prednisolone-equivalent dose (PED), using the potency equivalence listed in Table 5.2.

Table 5.2: Prednisolone-equivalent doses (PED) anti-inflammatory doses [280]

Glucocorticoid (GC)	Prednisolone-equivalent Dose (PED)
Prednisolone	***5mg***
Betamethasone	750mcg
Deflazacort	6mg
Dexamethasone	750mcg
Hydrocortisone	20mg
Methylprednisolone	4mg
Prednisone	5mg
Triamcinolone	4mg
Budesonide	5mg
Cortisone	25mg

Next, information on the frequency of GC use was extracted from the "dosage instructions" variable. Common key phrases were identified to classify the data into the different categories as listed in Table 5.3.

Table 5.3: Frequencies of oral GC administration

Frequencies	Examples of abbreviations / terms used in CPRD
Once a day	OD, ON, OM, once a day, everyday, daily
Twice a day	BD, BID, 1 MANE 1 NOCT, twice daily, 1 every 12 hours
Three times a day	TID, TDS, three times a day
Four times a day	QID, QDS
Five times a day	5X daily
Six times a day	6X per day
Every other day	EOD, every second day, alternate days
Weekly	Once a week, weekly, on day 6, every Monday
Twice weekly	Every third day, every 3 days, twice weekly
Three times a week	Three times a week, three times per week
Tapering	.....reduce by……, 6/5/4/3/2/1
When needed	PRN, as required, when necessary
Immediately	Stat, now, at once
As directed	As directed, as advised, as agreed
Unknown	-, --, ~, null

In cases where only the number of tablets per dose was given (e.g. 2 tablets), but not frequency, then it was classified as "unknown". The new frequency variable was then screened and rechecked manually to ensure that there were no errors.

The duration of each prescription was determined from the “duration of treatment” variable. If the duration of treatment was mentioned in the “dosage instructions” variable but not given in the “duration of treatment” variable, then the information was transcribed into the “duration of treatment” variable for use in the analysis. In cases where the duration information was not given, the following approaches were used:

1. Duration was determined by dividing the total quantity of GC tablets prescribed with the number of tablets per day. The number of tablets per day was determined by extracting information on the number of tablets per dose and frequency from the “dosage instructions” variable.
   Formula: Duration (days) = Quantity prescribed / Number of tablets per day

2. If the information in (1) was missing, then the duration was determined by calculating the difference in days between 2 consecutive prescriptions for each patient.
   Formula: Duration (days) = Date of Prescription 2 – Date of Prescription 1 (sorted by individual patients and date)

The treatment stop date was not given. As most prescriptions in primary care are usually prescribed for a period between 28 to 90 days, therefore, all prescriptions with a duration of more than 90 days were capped at the 90 days limit. Any missing durations were imputed with the median duration of all prescriptions in the dataset.

The next step in the data cleaning process was to apply some assumptions based on clinical practice – for example, if no information were provided for the daily dosing frequency, the default would be once a day as GCs are usually administered once a day. Similarly, if no information were given for the number of tablets per dose, then the default would be one tablet per dose. All “mg” and “ml” related dosing instructions were also scrutinized to ensure that they corresponded to the correct number of tablets/ oral solutions.

Next the “number of tablets per day” variable was determined according to the following rules:

1. Total quantity prescribed divided by the duration of each prescription
   Formula: Number of tablets per day = Quantity prescribed / Prescription duration

2. If the information in (1) was missing, then the number of tablets per day was determined by multiplying the number of tablets per dose with the daily frequency.
   Formula: Number of tablets per day = Number of tablets per dose * Frequency

The daily dose for each patient was then calculated by multiplying the number of tablets per day with the conversion factor for the calculation of appropriate PED and product strength. For subsequent analyses, I prepared the dataset in an interval format, of which the daily GC dose for the initial two years of follow-up was determined using loops in R.

5.5.4.2. Outcomes

The primary outcome of this study was DM. Patients with type 1 DM, defined as those who had a recorded Read code of type 1 DM, or were not on any oral anti-diabetic medications but merely prescribed insulin, were excluded from the study. For all patients who had a Read code or ICD-10 of any type of DM (other than type 1), the earliest date of any diabetes-related medications prescribed or any type of DM diagnosis received was set as the index date. The study population was then categorized into 3 groups, those with DM, no DM and pre-existing DM.

For this PhD project, I studied the effect of GC cumulative dose on DM in the initial two years of follow-up for the following reasons: firstly, the average duration for the treatment of PMR and GCA was reported to be approximately 2 years in previous studies [12, 11], therefore any DM occurring after that might be less likely to be GC-related. While it is possible that DM may have a delayed occurrence, it is unlikely considering the short elimination half-life (approximately two to four hours) of GCs, so the drug is likely to be cleared out of the system within a day (approximately five half-lives). Secondly, other studies have reported that the onset of GC-related DM was likely to be within the first two years of GC treatment [245, 281].

5.5.4.3. Baseline Characteristics

The next step of data management was to determine the baseline characteristics of the study population. Age at baseline was calculated by subtracting the date of birth of each individual from the study entry date. The age at baseline of my study population was also the age at the time of PMR and/or GCA diagnosis, as my cohort only included newly diagnosed patients. The ethnicity variable was re-grouped into 2 major groups: white and others (which includes mixed ethnicity, Asian, black etc) and a missing category were added to identify patients with unknown ethnicity.

I also looked at various baseline DM risk factors for type 2 DM, including smoking, BMI, and family history of DM. BMI was calculated by dividing weight in kilograms by height in meters squared. Some individuals had missing values for heights on some visits, so the height recorded in any other visits was used for all the visits with missing height data, as height for adults is unlikely to change over time, provided that the patient was at least 18 years old at the time of the measurement. For BMI, any value recorded before or on the date of study entry and within 1 year prior to study entry was considered to be BMI at baseline. The average of all values was calculated and labeled as BMI at baseline. In addition, I also categorized BMI into 2 groups: those who were obese (BMI >/= 30kg/m^2) and those who were not obese (BMI < 30kg/ m^2) or did not have any recorded BMI. The reason for including those who were not obese with those who did not have any recorded BMI was based on the assumption that those without any recorded BMI were more likely to have a normal BMI. It has been reported that underweight and overweight individuals were more likely to have their BMI recorded in primary care [282], thus contradicting the missing at random assumption. Another study reported that 97% of patients with a record of type 2 DM had a recent BMI recorded in CPRD [283], further supporting the possibility that those who did not have any recorded BMI were likely not obese as obesity is a known risk factor for type 2 DM. For smoking status, the smoking status recorded before or on the date of study entry and within 1 year prior to study entry was considered as baseline smoking status. For patients with multiple smoking statuses, the highest level of exposure was determined in the following order: current smoker, former smoker and non-smoker. All smoking status codes recorded at baseline and before the year prior to entry were checked and the highest level of exposure (ranked in the following order: current smoker, former smoker and non-smoker) was selected. Similarly, all smoking status codes recorded in the year after the date of entry were checked, and the highest level of exposure was chosen as post-baseline smoking status. Unlike BMI that is likely to vary over time, smoking status is less likely to change drastically over time; therefore for patients

without any smoking information at baseline, the method of last observation carried forward (from pre-baseline) or backwards (from post-baseline) was used. For the rest of the study population without any smoking information, their smoking status was categorized as unknown. Since family history is a strong risk factor for DM, I also included this variable in my baseline characteristics. Lastly, any non-oral GC use during the study follow-up duration was also determined. Both family history of DM and non-oral GC use during follow-up are potential confounders that were adjusted for in later analyses.

5.5.5. Missing Data

Since information had already been collected, the quality of the study is reliant on the completeness of the data collected. Missing data are problematic for all observational research, particularly in routinely collected data [284]. It may result in selection bias if variables needed to define the study cohort are not missing at random, or if identifiers required for linkage are missing. The way on how missing data should be handled is challenging – restriction to those with only complete data may introduce bias, while multiple imputation may also not be appropriate because the pattern of missingness may not be missing at random. For example, approximately two thirds of BMI data were missing in my study; but BMI have been reported to be recorded more frequently in patients at risk of developing DM as compared to the general population [282]. This suggests that data may not be missing at random; therefore multiple imputation may not be appropriate in this case. In this case, BMI was only reported in the baseline characteristic table and not used in any of the other analyses, therefore I did not do any imputations.

For PMR patients with missing prescription durations, the median duration of all prescriptions for PMR patients was used. The same rule was applied for patients with GCA or with both PMR and GCA. Other studies have used a different approach - one study replaced any missing prescription duration with the average of that patient's duration for other prescriptions of the same drug with the same strength (if present); or the average duration of all other patients' prescriptions of the same drug with the same strength [12]. There are however, some limitations with this approach as the prescription duration of each patient may differ over time according to different circumstances. For example, some patients may be prescribed with longer duration of GCs at different times of the year as they travel for vacation. Using the average duration of all other patient's prescriptions of the same drug has its limitations as well, as some patients with limited mobility may have been prescribed with longer durations

to minimize the number of visits needed. Since there is no one best method to account for missing prescription durations, the median imputation was used, as it is less susceptible to any outliers that the other methods may present with. Missing data for dosing frequency and number of tablets per day have been discussed in detail in the preceding section (Section 5.5.4.1). I did consider doing a sensitivity analysis using complete case analysis, but it would be unlikely to obtain a large enough sample of cases with no missing data as the main reason for missing data in the prescription database was because all patients were managed in secondary care rather than primary care, of which information relating to secondary care were unavailable.

5.6. Statistical Analysis

5.6.1. Descriptive Analysis on Baseline Characteristics

Baseline characteristics of the study population were summarized using descriptive statistics – median and inter-quartile range (IQR), or mean and standard deviations (SD) for continuous variables, and frequency, percentage for categorical variables. For continuous variables with a skewed distribution (e.g. age and follow-up duration), I used the median and IQR; while for variables with a normal distribution (e.g. BMI), I used the mean and SD. Baseline characteristics were presented for patients with PMR only, GCA and PMR/GCA, as well as for the overall study population. I chose to analyze PMR patients as a stand-alone group, and categorize those with GCA and both PMR and GCA as another group. Patients presenting with both PMR and GCA usually receive the same high-dose GC regimen as patients with GCA only, with the rationale that they are considered to be at a similar risk of vascular complications. Therefore, the impact of GC treatment on the risk of DM would likely be comparable. In addition, grouping them together will also add to the robustness of statistical analyses, as the number of patients with both PMR and GCA was relatively small compared to those with PMR alone or GCA alone.

5.6.2. Descriptive Analysis on Prescription Database and Prescribing Patterns

Information from the prescription database was also presented using summary statistics, including the types of oral GC prescribed in primary care and dosing frequencies of oral GCs. The percentages of missing data for key variables needed for the calculation of GC dose were also determined and compared with the CPRD derived dataset. I also calculated the total duration of treatment, cumulative dose, first dose, monthly starting dose and average daily dose. The total duration of treatment was calculated as the sum of all prescription durations for each patient. The cumulative dose was calculated as the sum of quantity prescribed, multiplied by strength and PED for all prescriptions for each patient. The first dose was the total dose of the first prescription of each patient, while the monthly starting dose was the total dose for the first month of treatment of each patient. The average daily dose was calculated as the total cumulative dose divided by the total duration of treatment for each patient.

I also looked at the prescribing pattern of oral GCs for PMR and/or GCA patients in primary care over the initial two years of PMR/GCA diagnosis, presented in the form of total monthly oral GC dose, high dose (75^{th} percentile) versus low dose regimen (25^{th} percentile) and average monthly oral GC dose. A comparison between real-world GC prescribing pattern in the initial twelve months of treatment and European League Against Rheumatism (EULAR) recommended guidelines was also made for these patient populations [22, 21].

5.6.3. Kaplan Meier Survival Curves

Survival analysis, also known as the time to event analysis, focuses on the distribution of survival time and models the time it takes for events to occur within a specified time interval. For my PhD, the “event” was newly diagnosed DM, and the time interval was specified to be within the first two years of PMR and/or GCA diagnosis. There are several methods to estimate a survival (or hazard) function, of which the Kaplan-Meier (KM) curve is one of the most used methods. For the KM curve, there are no assumptions about the baseline hazard distribution. Therefore, it imposes the least structure and is relatively easier to estimate and interpret. However, it is mostly descriptive in nature as it is difficult to incorporate predictors. The log rank test is often used to test the null hypothesis of no difference in survival between groups. In other words, it can be thought as a test of measuring whether the survival curves are identical (or overlapping) or not. It is conducted by assigning a “1” to the event of interest (e.g. DM) and a “0” to all competing risk events and censored observations. A

p-value of more than 0.05 indicates that the two survival curves are different and the null hypothesis should be rejected.

For my PhD, I used the survival Kaplan Meier methods and log rank test to compare the risk of DM in patients with PMR and/or GCA, stratified by underlying disease, gender and age group. Age group was categorised using tertiles, quartiles and quintiles.

5.6.4. Extended Time-varying Cox Model for Cumulative Dose

Survival analysis can also be extended to assess several risk factors or exposures simultaneously, in relation to survival time. One of the most popular techniques for this is the Cox proportional hazard regression. In a Cox proportional hazard regression model, the measure of effect is the hazard rate, which is the risk of failure (or the event of interest such as DM), given that the participant has survived up to a specific time [285]. The Cox proportional hazard model is also called a semi-parametric model, because there are no assumptions about the shape of the baseline hazard function, but there are, however, several important assumptions for appropriate use of the model. The assumptions include independence of survival times between each individual in the cohort, a linear association between the natural logarithm of the relative hazard and predictors, and that changes in predictors produce proportional changes in the hazard regardless of time.

One of the major limitations of the Cox proportional hazard model is that the hazard ratio is averaged over event times. In other words, when estimating the overall hazard ratio over the follow-up duration, the same weights are given to the very early hazard ratios that affect almost all individuals, as are given to very late hazard ratios affecting only the few individuals still at risk. However, the guidelines recommend starting at a high GC dose and tapering this dose down over time. DM risk associated with GC therapy is thought to be higher at higher GC doses. Therefore, use of the extended time-varying Cox is more appropriate as it allows incorporation of covariates that change over time into the model. It allows the comparison of the current GC dose of each patient who had the event to the GC doses of all others who were at risk at each event time [286].

The main objective of this PhD was to explore the association between GC dose exposure during the first two years of treatment and the risk of developing DM, of which the following variables were adjusted in the model: family history of DM and use of non-oral GC during the study duration. The goal was to use a parsimonious model with a minimum number of parameters; therefore only variables that were clear confounders were included. Age and BMI were not included in the model because while they may be associated with the risk of developing DM, they were unlikely to be associated with the use of GC for the treatment of PMR and/or GCA. In addition, slightly more than half of the patients did not have a recorded BMI, and while the use of multiple imputation could have been used to address the issue of missing data, it may not be appropriate for this study as studies have reported that BMI data were not likely to be missing at random in primary care [282, 283]. The use of complete case analysis would have resulted in a much reduced sample size.

Non-linearity of GC dose was tested using the ANOVA analysis of deviance test by comparing two models, one with and the other without the quadratic term. The best fitting model was selected.

I used two different approaches to examine the association of oral GC cumulative dose and DM using the extended time-varying Cox model. Firstly, the risk of DM was quantified based on each gram increase in cumulative GC dose within the initial two years of PMR/GCA diagnosis. Secondly, the risk of DM was quantified using survival percentiles [287], of which patients who were on high dose (using the upper quartile or 75^{th} percentile) were compared with those who were on low dose (lower quartile or 25^{th} percentile) within the initial two years of PMR/GCA diagnosis.

There were a few reasons why I chose to compare the risk of DM between those on high GC dose versus low GC dose. Firstly, since my study only includes newly diagnosed PMR and/or GCA patients, all of them would have been on GC therapy, thus I was unable to compare the risk with patients not on GC therapy. Secondly, the Interpretation of survival percentiles is easier and more intuitive, thus providing additional value and facilitates the translation of results from epidemiological studies into clinical practice. Another advantage is that it is well suited to evaluate situations in which the association of interest is changing over time. In other words, the association between varying GC doses with the risk of developing DM can be evaluated over time through focusing on the selected percentiles of observed distribution of events, without necessarily assuming a constant effect.

5.6.5. Rolling Cumulative Dose Model

While the extended time-varying Cox model allows the incorporation of GC cumulative dose to vary over time, it does not account for the timing of GC exposure. In other words, it does not indicate whether the more recent GC doses had a more significant effect on the risk of developing DM as compared to doses from a distant past. To explore whether the timing of GC exposure actually affects the risk of developing DM, I used the “rolling window calculations”, of which rolling calculations of cumulative GC dose were applied to a fixed width subset of the data (also known as the window). The rolling cumulative dose method allowed visualization of how the impact of cumulative dose changes over time, and by varying the window (in this case, months following the diagnosis of PMR and/or GCA), I was able to determine the timing of the most recent GC exposure that had a largest impact on risk of DM. The best fitting model or optimal rolling window timeframe was determined by comparing the concordance index, of which the highest concordance index was chosen. The coefficient of that best fitting model was determined and applied to calculate the hazard ratios for patients with high GC dose versus low GC dose over the initial two years since PMR/GCA diagnosis.

5.6.6. Weighted Cumulative Exposure (WCE) Model

While the rolling cumulative dose analysis is a useful method to determine the risk based on recent cumulative doses, it has its limitation as the time-dependent hazard is fixed for each time window. To address this limitation, I used another statistical method, namely the WCE analysis that allows the assessment of risk based on the dose, duration and timing of treatment.

Breslow et al [288] and Thomas [289] first introduced and discussed the concept of weighted cumulative exposure (WCE) that combines information about dose, duration and timing of exposure into a summary measure. Vacek [290] then proposed a parametric modeling of the weight function in case-control studies, which was then further developed by Abrahamowicz et al [291], who used the parametric WCE framework within the Cox’s proportional hazard model to refine the assessment of the associations between exposure and outcome. However, modeling strategies that impose a specific parametric form of the weight function in the absence of solid prior knowledge about its shape may lead to invalid results if the function is incorrectly specified [290]. With that in mind, Sylvestre et al [292] proposed the regression spline-based method for modeling the WCE as a time-dependent covariate in the Cox’s proportional hazard regression analysis of cohort studies. Splines are flexible

mathematical functions defined by piecewise polynomials joined at points on the x-axis known as knots. Regression splines are particularly useful because they can be incorporated into any regression model that has a linear predictor, and they are also relatively simple but still have enough flexibility for most practical data [293].

A WCE analysis models the time-dependent hazard as a smooth flexible function of time. Taking the time-varying use of GC as an example, X_{GC} (t) is the dose of GC at time t. The joint effect of past doses of GC at the index date u is given by the time-varying WCE metric [292]:

$$\mathrm{WCE}(u) = \sum_{t}^{u} w(u-t)X(t)$$

where $t \leq u$ indexes times of GC exposure preceding u and where w(u-t) is the function assigning weights to past GC daily doses based on the time elapsed since the last dose was taken. In other words, at any point during the follow-up, the cumulative dose will be calculated as a weighted mean of the past doses, with higher weights assigned to more recent doses. The shape and the values of the weight function w(u-t) are unknown but they can be estimated from the data by the metric below:

$$w(u-t) = \sum_{j=1}^{m} \theta_j B_j(u-t)$$

where Bj, j=1,….,m, represent the m functions in the cubic spline basis and θj, j=1,…,m, represent the estimable coefficients of the linear combination of the basis splines. By using the flexible cubic B-splines, the model avoids the need to specify a-priori the analytical form or shape of the weight function. The WCE weight plots over time provide great clinical insight on the etiologically pertinent time window of past exposure and on the relative importance of doses taken at different time periods [294, 250, 291, 295]. This is particularly useful to help unravel the possibly complex mechanisms linking drug exposure to adverse events and help clinicians decide on how treatment regimens may be optimized to improve the risks versus benefits ratio in clinical practice.

The best-fitting WCE model was selected based on the lowest Bayesian Information Criterion (BIC) value. As with all the other analyses, the hazard ratio for the best fitting model was compared between those on high dose versus those on low dose over the initial two years since PMR/GCA diagnosis. All analyses were carried out in R Version 3.3.1. Results from my analyses will be presented in the next chapter.

CHAPTER 6: RESULTS

6.1. Overview

This chapter reports the results from the analyses of the inception cohort together with a brief description of the patient selection process, followed by the baseline characteristics of newly diagnosed patients, stratified by disease status. The next sub-section will include a detailed description of the prescription database, followed by oral glucocorticoid (GC) prescribing patterns in primary care compared with European League Against Rheumatism (EULAR) guidelines. The final sub-section will report the quantification of diabetes mellitus (DM) risk associated with oral GC dose using the extended time-varying Cox, rolling cumulative dose and weighted cumulative exposure models.

6.2. Patient Selection Process

Figure 6.1 shows the flow of patients through the data extraction process. Approximately 29.9% of the patients were excluded due to patient related factors, of which 11.9% had pre-existing DM, including type 1 DM, type 2 DM, secondary DM, unspecified DM and steroid induced DM. As this was an inception cohort, all patients with a pre-existing diagnosis were excluded from the study, accounting for approximately 18.0%. Another 11.6% of patients were excluded due to treatment related factors, of which 3.8% never had any GC prescriptions. Approximately 4.6% had no recorded prescriptions during the study follow-up duration, while another 3.2% had no recorded oral GC prescriptions, thus they were all excluded from the study. A total of 23048 patients were included in the final cohort.

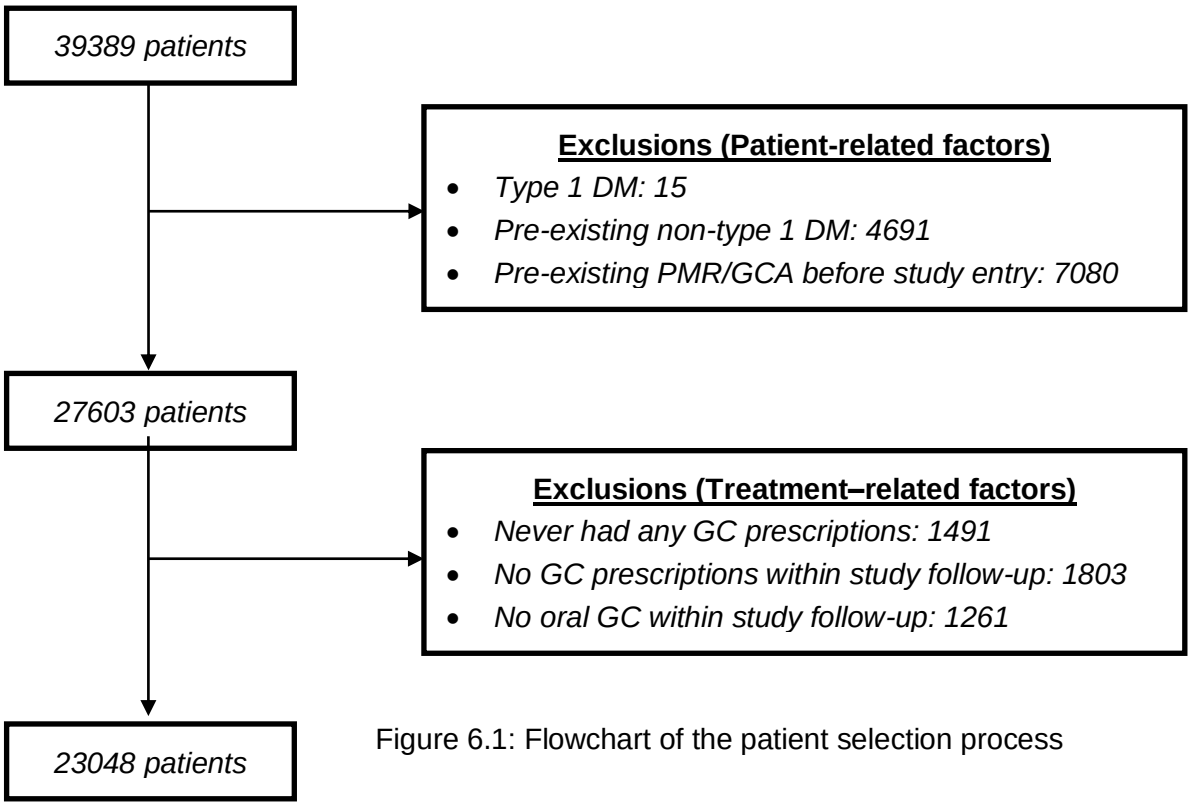


Figure 6.1: Flowchart of the patient selection process

6.3. Baseline Characteristics

Table 6.1: Characteristics of newly diagnosed patients, stratified by disease status

Patient Characteristics	All (n=23048)	PMR (n=19204)	GCA with or without PMR (n=3844)
Age at diagnosis of PMR/GCA, years			
Median	74.1	74.3	73.2
(IQR)	(66.8-80.2)	(66.9-80.3)	(66.2-79.6)
Follow-up duration, years*			
Median (IQR)	4.5 (2.0-7.8)	4.5 (2.1-7.8)	4.4 (1.9-8.1)
Gender, n (%)			
Females	15706 (68.0)	12908 (67.2)	2762 (71.9)
Ethnic group, n (%)			
White	20746 (90.0)	17211 (89.6)	3535 (92.0)
Others	401 (1.7)	297 (1.5)	104 (2.7)
Index of multiple deprivation (IMD), quartiles, n (%)**			
1 (Least deprived)	6079 (26.4)	5158 (26.9)	921 (24.0)
2	6266 (27.2)	5329 (27.7)	937 (24.4)
3	5836 (25.3)	4800 (25.0)	1036 (27.0)
4 (Most deprived)	4866 (21.1)	3917 (20.4)	949 (24.7)
Smoking, n (%)			
Current	2908 (12.6)	2263 (11.8)	645 (16.8)
Former	6259 (27.2)	5295 (27.6)	964 (25.1)
Never	7971 (34.6)	6704 (34.9)	1267 (33.0)
Body mass index (BMI), kg/m^2,			
Mean (SD)	27.2 (5.3)	27.3 (5.3)	26.7 (5.4)
Family history of DM, n (%)	1360 (5.9)	1133 (5.9)	227 (5.9)
Non-oral GC use during follow-up*, n (%)	10259 (44.5)	8464 (44.1)	1795 (46.7)
Total oral GC cumulative dose over entire follow-up duration*, g,			
Median (IQR)	4.2 (2.0-8.0)	4.1 (2.0-7.6)	5.3 (2.0-10.4)
Oral GC cumulative dose within first two years of PMR/GCA diagnosis*, g,			
Median (IQR)	3.5 (1.8-5.3)	3.4 (1.8-5.1)	4.4 (1.8-7.0)

Missing data (%): Ethnic group, 8.2%; BMI, 64.1%; Smoking, 25.6%
**Follow up ceases on diagnosis of DM*
***IMD categories were based on the overall distribution within the CPRD population*

Table 6.1 describes the baseline characteristics of newly diagnosed patients, stratified by disease. PMR was the most common diagnosis (83%), followed by GCA (11%) and approximately 6% was diagnosed with a combination of both PMR and GCA. Patients with PMR and patients with GCA (with or without PMR) were similar in terms of age, sex, ethnicity and family history of DM.

Data on socio-economic status (see Table 6.1, index of multiple deprivation, IMD) suggest that PMR is under-represented in the most deprived quartile (as shown by the difference of 6.5% between the least deprived and most deprived quartiles), and similarly common in quartiles 1-3.

The percentage of current smokers was 5% higher in the GCA (with or without PMR) group as compared to the PMR group. The mean BMI at baseline in both groups were indicative of an overweight population, which was reflective of the general population in England. The 2017 Health Survey for England reported that the mean BMI among adults was 27.7kg/m^2 [296]. According to the World Health Organization (WHO) classification, overweight is defined as having a BMI between 25.0-29.9kg/m^2, and obesity is defined as $\geq$ 30 kg/m^2. Of the 36% patients with a recorded BMI at baseline, approximately 63% had a BMI higher or equal to 25kg/m^2, suggesting that there is a possibility that overweight or obese patients were more likely to have a recorded BMI; while those with no recorded BMI may have had a normal BMI. Nearly half of the study population had some use of non-oral GC therapy during follow-up. The median total oral GC cumulative dose over the entire follow-up duration was approximately 4.2g (IQR 2.0-8.0g) in the overall cohort, and 3.5g (IQR 1.8-5.3g) over the initial two years since PMR/GCA diagnosis, suggesting that the extent of GC exposure is much higher in the first two years of follow-up. Total oral GC cumulative dose in patients with GCA (with or without PMR) was higher than in patients with PMR, as a higher dose is needed to treat symptoms and vascular complications of GCA.

6.4. Prescription Database

There were approximately 1 million prescriptions available between the start of study entry date and end of follow-up, of which 232,506 prescriptions (20.4%) were non-oral GC. These were not taken into account for the calculation of the exposure variable used in my analyses, as my primary objective was to study the effects of oral GC on the risk of DM.

6.4.1. Types of Oral GC Prescribed

There were 68 different oral GC products in the prescription database, consisting eight types of GCs with different anti-inflammatory potency.

Table 6.2: Types of oral GCs prescribed in primary care

Types of Oral GC	Number of prescriptions, n (%)
Prednisolone*	648,481 (99.5)
Dexamethasone	1299 (0.2)
Hydrocortisone	1053 (0.2)
Budesonide	345 (0.1)
Betamethasone	291 (<0.1)
Prednisone*	265 (<0.1)
Deflazacort	150 (<0.1)
Methylprednisolone	7 (<0.1)
Total	**651,891 (100.0)**

**GCs generally recommended in treatment guidelines to treat PMR and/or GCA*

Table 6.2 shows the eight types of GCs with different anti-inflammatory potency prescribed in primary care over the study duration. The two GCs generally recommended in treatment guidelines to treat PMR and GCA were prednisolone and prednisone, which accounted for approximately 99.5% of the entire prescription database used in my analyses.

6.4.2. Missing Data for Key Variables

There were four variables in the prescription database that contained information essential for data analyses – quantity of GC prescribed, name of product prescribed, prescription duration and “dosage instruction”. These variables were listed separately as stand-alone variables in the database and extracted directly from primary care. The variable “dosage instruction” contained free text as documented by general practitioners (GPs) in primary care, of which most of the information relating to dose and frequency were recorded. In addition to these four variables, there were another two variables derived by CPRD, namely the “daily_frequency” (dosing frequency) and “daily_dose” (number of tablets per day). For this PhD, instead of using the two CPRD-derived variables listed above, I created another two variables (1) dosing frequency and (2) number of tablets per day from the information given in the “dosage instruction” variable. My extracted dosing frequency and number of tablets per day variables were then compared to the CPRD-derived frequency and number of tablets per day variables.

I first applied a rule-based approach for all common “dosage instruction” using the statistical software R. For example, the dosing frequency for all “OD” prescriptions was preset as “once-a-day”. There were however, many typos and misspellings in the free text of the “dosage instruction” variable, of which manual screening was required for better accuracy. Of the initial 1 million prescriptions in the prescription database, there were 4182 unique “dosage instruction” that required manual screening. Information for daily dosing frequency and number of tablets per day was first extracted, and then rechecked on four separate occasions (January, March, June 2018 and August 2019) to ensure that the categories were properly coded. The extracted data was then contrasted and compared to the CPRD-derived data.

Table 6.3: Comparison of missing data for key variables in the prescription database

Key Variables	Extracted Data From Primary Care*	CPRD-derived**
	Missing data, n (%)	
Quantity prescribed	123 (0.0)	123 (0.0)
Product name	0 (0.0)	0 (0.0)
Duration	631,453 (96.9)	632,697 (97.1)
Dosing frequency	351,426 (53.9)	348,498 (53.5)
Tablets per day	376,782 (57.8)	358,246 (55.0)
Total	**651,891 (100.0)**	

**Extracted data from primary care refers to the data I extracted from primary care data collected directly from registered primary care GPs*
***CPRD derived data refers to the data that has been managed by the CPRD team*

A summary of the distribution of missing data for the five important variables is shown in Table 6.3. The quantity of oral GC prescribed was a well-recorded variable, with only 0.02% missing data, and this was consistent with another two studies [297, 12] that reported a 99.3% and 99.9% of valid quantity value in drug exposure respectively. The product name (or GC name) was well documented, with no missing data as this variable was automatically extracted through scanning without the GP having to enter the information. This variable was crucial for determining the dosage strength and prednisolone-equivalent dose (PED) in the later stages of the analyses. The percentage of missing data in the “duration” variable was very high, as this was not a required field for GPs to fill out in the database. This finding was fairly consistent with above-mentioned study [297], which reported a missing value of 93%. I derived an additional 1244 duration values (0.2%) using the information recorded in the “dosage instruction” variable. In other words, if the duration was mentioned in the “dosage instruction” variable, but not given in the “duration” variable, then the information was extracted for use in subsequent analyses. Information on “daily dosing frequency” and “number of tablets per day” appeared to be more complete in the CPRD-derived dataset, because in the CPRD-derived dataset, when no information was provided on

the number of tablets per day, one tablet was assumed, but only in some cases. There was however, no consistency and no obvious pattern on how this was determined in the CPRD-derived dataset. As above, a “once a day” dosing frequency is assumed for the CPRD-derived dataset if no information was available, though again, there was no consistency and no obvious pattern on how this was determined. For my extracted data, the number of tablets per day was assumed to be one if no information was available. Similarly, the daily dosing frequency was also assumed to be one if no other information was available.

6.4.3. Dosing Frequencies

Table 6.4: Distribution of dosing frequencies in the prescription database

Dosing Frequencies	Extracted Data From Primary Care*	CPRD-derived**
	Number of Prescriptions, n (%)	
Once a day	283,231 (43.4)	297,366 (45.6)
1.5 times per day	-	62 (0.0)
1.67 times per day	-	2 (0.0)
Twice a day	3,240 (0.5)	3,187 (0.5)
2.5 times per day	-	1 (0.0)
Three times a day	1,594 (0.2)	2,267 (0.3)
3.5 times per day	-	2 (0.0)
Four times a day	487 (0.1)	492 (0.1)
Five times a day	5 (0.0)	8 (0.0)
Six times a day	6 (0.0)	6 (0.0)
Every other day	3,645 (0.6)	-
Once weekly	109 (0.0)	-
Twice weekly	60 (0.0)	-
Three times a week	9 (0.0)	-
Tapering	4,588 (0.7)	-
When needed	3,483 (0.5)	-
Stat/Immediately	8 (0.0)	-
As directed	161,399 (24.8)	-
Unknown	190,027 (29.2)	348,498 (53.5)
Total	**651,891 (100.0)**	

**Extracted data from primary care refers to the data I extracted from primary care data collected directly from registered primary care GPs*
***CPRD derived data refers to the data that has been managed by the CPRD team*

Table 6.4 shows the distribution of dosing frequencies recorded in the prescription database. The three most common dosing frequencies were “once a day”, “as directed” and “unknown”, which accounted for 97.4% of the prescription database. About one fourth of the prescriptions were “as directed” prescriptions, which meant that the dose and/or dosing frequency were not specified, but patients were instructed to “take as directed” verbally. In some cases, the dose was specified, but not the dosing frequency, and vice versa. All prescriptions were categorized as “unknown” if they did

not contain any information on the specific dosing frequency, and no instruction on "take as directed" was indicated. The total number of prescriptions categorized as "once a day" was about 2.2% higher in the CPRD-derived dataset, as compared to the variables I created using the information collected from primary care data. This was partly because some prescriptions involving "every other day", "weekly" or "multiple times weekly" dosing were categorized as "once a day" in the CPRD-derived dataset. Another reason was due to the fact that if the dosing frequency were unknown, it would be categorized as "once a day", but only in some cases.

As mentioned in Section 6.4.2, I also applied certain assumptions that correlated with clinical practice in my subsequent analyses, which included the assumption that the dosing frequency would be once a day if any of the following directions were recorded in the primary care data: "tapering regimens", "when needed", "stat/immediately", "as directed", or "unknown". The application of this assumption resulted in 98.6% of the prescriptions having a "once a day" dosing frequency.

6.4.4. Duration of GC Prescriptions

As discussed in Section 6.4.2, the "duration" variable was not well recorded in primary care, with only approximately 3% of the prescription database having a recorded duration value. Despite the large number of missing data in the duration variable, there were other ways of deriving information on duration by using a combination of other variables in the database that was explained in detail in the previous chapter. After applying all the various approaches detailed in Chapter 5 (Section 5.5.4.1), approximately 1.7% of prescriptions still had a missing duration due to insufficient information. The median duration for prescriptions with a quantifiable duration for PMR, as well as GCA (with or without PMR) was 28 days. Therefore, for the 1.7% of prescriptions that had a missing duration, the duration was replaced with the median of 28 days. Approximately 4.9% of the prescriptions had a duration of more than 90 days, which is unlikely as most prescriptions in primary care were usually prescribed for a period between 28 to 90 days as GPs are strongly recommended by the National Health Service (NHS) to not prescribe medications for more than three months. To address this issue, all prescriptions that had a duration of more than 90 days were capped at the 90 days limit.

The median duration of treatment was approximately 1.7 years (IQR: 0.7-3.5 years) in the PMR group and 1.5 years (IQR: 0.4-3.5 years) for the GCA (with or without PMR) group.

6.4.5. Number of Tablets Per Day and Daily Dosing

Approximately 2.5% of the prescription data had a daily dose of less than 1mg, of which 0.8% had a daily dose of less than 0.5mg. On the other hand, approximately 0.6% had a dose of more than 120mg/day. One plausible explanation for these very high dose prescriptions was pulse therapy for GCA patients with threatened or established visual loss at diagnosis. This is possible but unlikely, as these were all oral prescriptions; therefore the maximum daily dose for these prescriptions was capped at 120mg.

The median average daily dose of GC prescribed for the entire follow-up duration in the practice was 6.6mg/day (IQR: 5.0-9.6mg/day) and 9.8mg/day (IQR: 6.5-17.3mg/day) for the PMR group and GCA (with or without PMR) group, respectively.

6.5. GC Prescribing Patterns

The results for this section present the oral GC prescribing patterns for two groups of patients – those with PMR, and those with GCA (with or without PMR) over the first two years since the diagnosis of PMR/GCA. The results are summarized in the forms of total monthly oral GC dose, high dose (75^{th} percentile) versus low dose regimen (25^{th} percentile) and average monthly oral GC dose. The prescribing pattern in primary care was also compared against EULAR guidelines for the different diseases respectively.

6.5.1. Total Monthly Oral GC Dose

Figure 6.2 presents the box plots of total monthly oral GC dose prescribed to PMR patients over 24 months. As expected, there was a decreasing trend in the total monthly oral GC dose prescribed over time. The initial total dose in the first month was 714mg in the upper quartile, compared to 263mg in the lower quartile. The range of total monthly oral GC doses was more varied in the first twelve months, as shown by the monthly box plots. It is also worth noting that after 18 months since diagnosis, half of the patients were no longer on GC treatment (as shown by the total GC dose of zero). The long upper whisker across the months indicates that the doses were more varied in the upper quartile as compared to the lower quartile. Outliers were present, of which there were some total monthly doses exceeding 3g in the initial stages of follow-up.

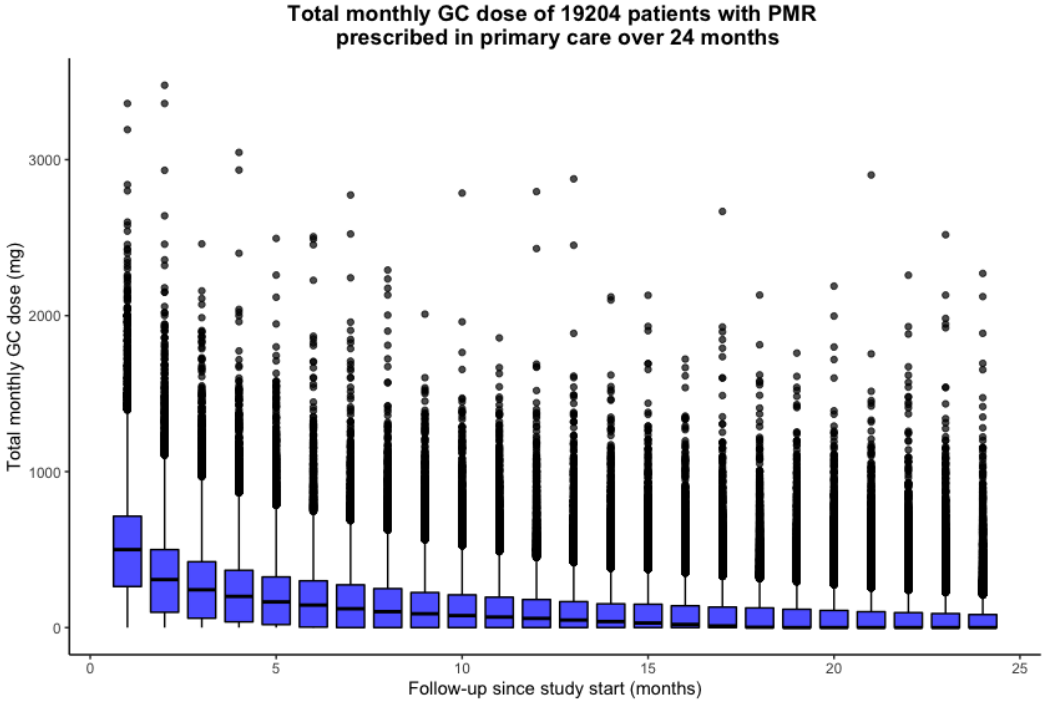


Figure 6.2: Total monthly oral GC in PMR patients over 24 months

Figure 6.3 presents the box plots of total monthly oral GC doses in patients with GCA (with or without PMR) over 24 months. There was a decrease in the total monthly oral GC doses prescribed over time. The initial total dose in the first month was higher compared to the PMR group, starting at approximately 1050mg in the upper quartile and 200mg in the lower quartile. The range of total monthly oral GC doses was more varied in the first 12 months, as suggested by the comparatively taller box in the box-plot. As with the PMR group, half of the patients were no longer on GC treatment after 18 months. The long upper whisker across the months indicates that the doses were more varied in the upper quartile as compared to the lower quartile. Outliers were also present in this patient population, of which there were some total monthly doses exceeding 3g in the initial stages of follow-up.

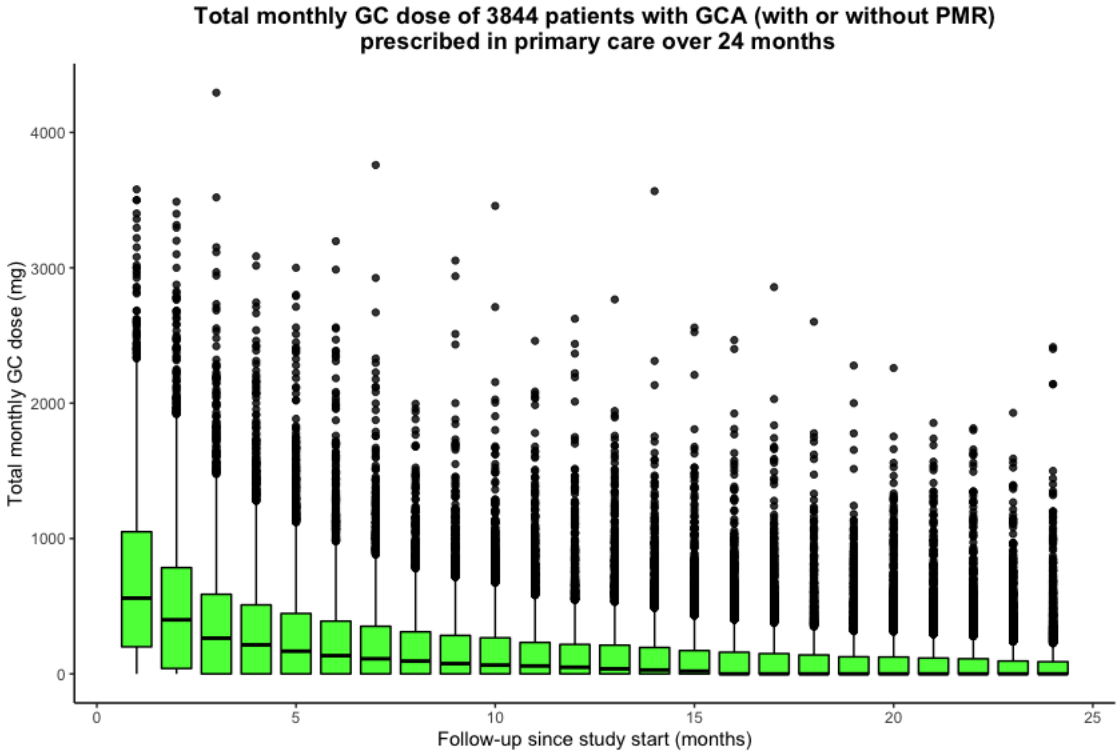


Figure 6.3: Total monthly oral GC in GCA (with or without PMR) patients over 24 months

6.5.2. High Dose (75th Percentile) Versus Low Dose (25th Percentile) Regimens

Figure 6.4 presents the prescribing trend of patients on high GC dose versus those on low GC dose, defined by the 75th percentile and 25th percentile respectively. Approximately 75% of patients with PMR were prescribed with less than 714mg/month (23.8mg/day) in the initial month of treatment, and one fourth of PMR patients stopped GC treatment by the sixth month. For patients with GCA (with or without PMR), 75% of them were prescribed with less than 1050mg/month (35mg/day) in the initial month of treatment, with one fourth of patients no longer on GC treatment after the third month. The purpose of Figure 6.4 is to describe the dose regimen in primary care practice, specifically looking at the range of patients who were on high dose and low dose GC. It is likely that patients on high dose GC were at higher risk of developing DM, therefore this stratification of high dose versus low dose GC users is important for risk assessment between the two groups.

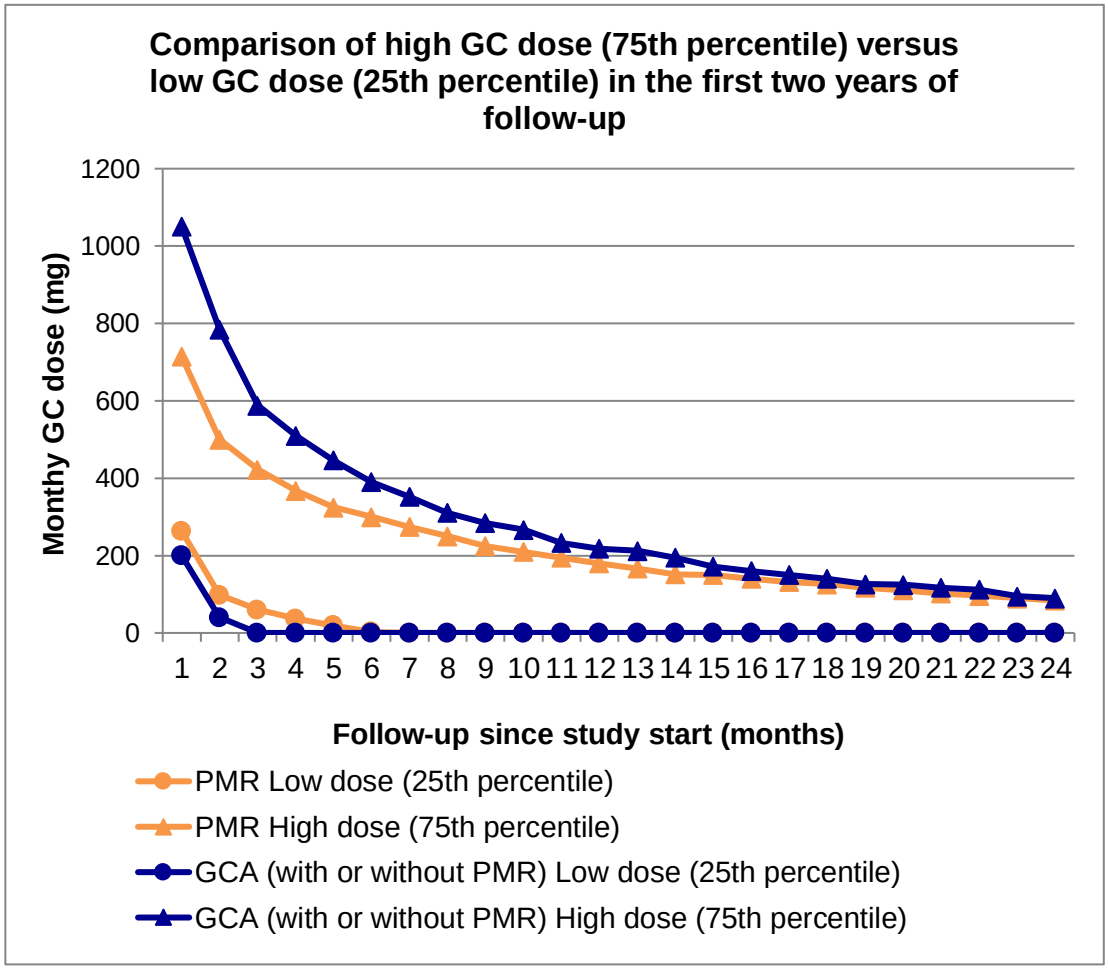


Figure 6.4: Comparison of high GC dose (75th percentile) versus low GC dose (25th percentile) among PMR and/or GCA patients within the first two years of diagnosis

6.5.3. Average Total Monthly Oral GC Dose

Figure 6.5 presents the average total monthly oral GC dose over 24 months for PMR patients in primary care, stratified by DM status. Curves were fitted using the added smoothed conditional regression line. Patients who developed DM generally had higher GC doses throughout the course of treatment, starting with high doses, which were tapered over time. The difference in GC dose between patients who developed DM and those that did not develop DM was higher after six months of diagnosis. The highest average total monthly oral GC dose for DM patients was 520mg and 517mg in the non-DM group in the first month after diagnosis.

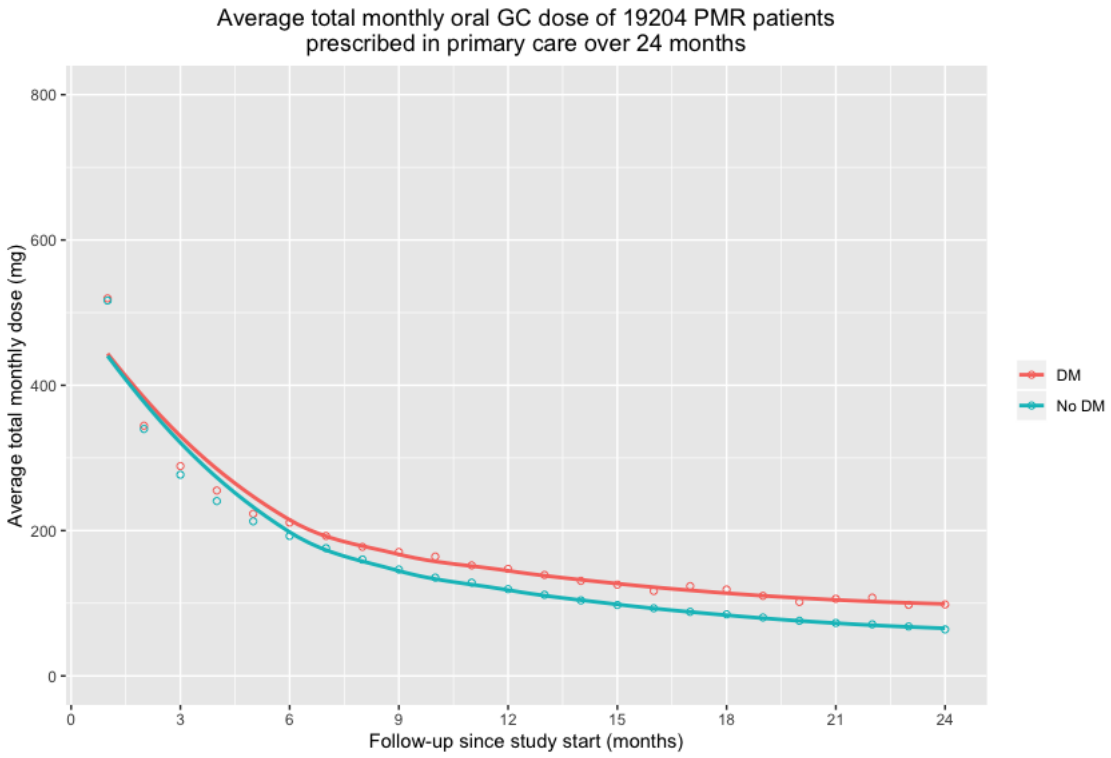


Figure 6.5: Average total monthly oral GC prescribing pattern over 24 months for PMR patients, stratified by DM status

Figure 6.6 presents the average total monthly oral GC dose over 24 months for patients with GCA (with or without PMR) in primary care, stratified by DM status. DM patients had a higher GC starting dose and showed a slower tapering trend after month nine, compared to the non-DM group. The highest average total monthly oral GC dose for DM patients was 730mg and 696mg in the non-DM group in the first month after diagnosis.

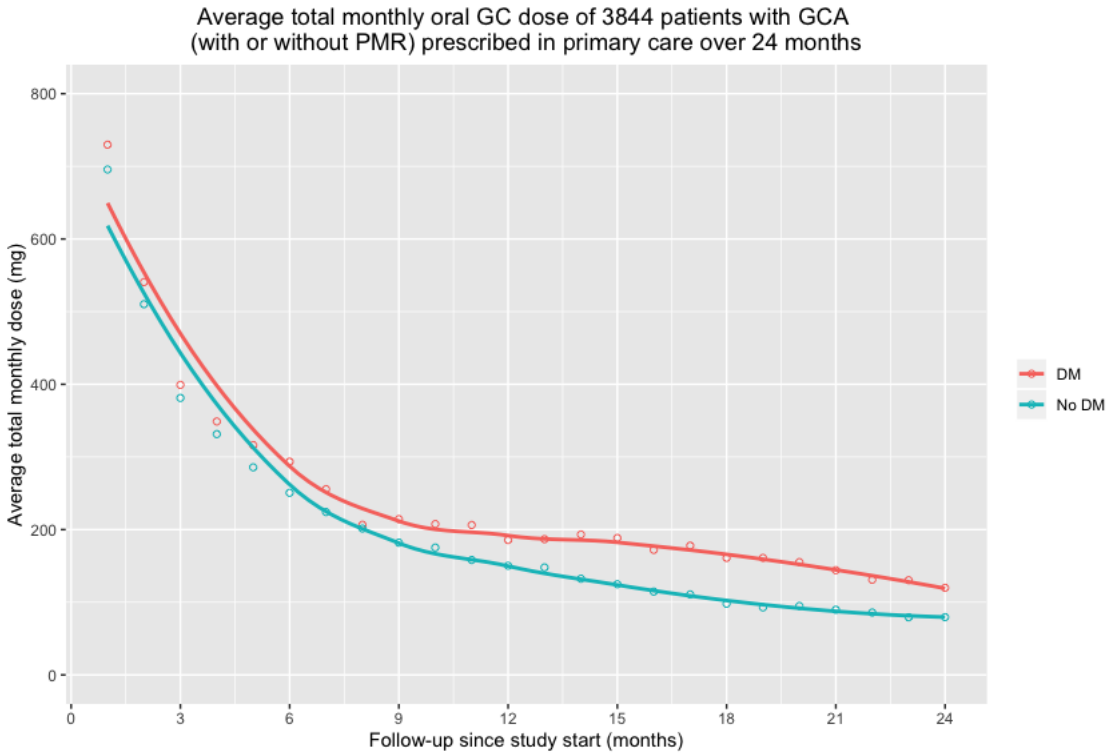


Figure 6.6: Average total monthly oral GC prescribing pattern over 24 months for patients with GCA (with or without PMR), stratified by DM status

Figures 6.5 and 6.6 are a depiction of the distribution of dosing for those with and without DM. These plots were however not used for interpretation, as there were some issues with it. For example, even though DM patients seemed to have a much higher dose in month 18 compared to non-DM patients, it does not really depict the actual dosing of all DM patients as only those who were still in the cohort were taken into consideration.

6.5.4. GC Prescribing Patterns in Primary Care vs. EULAR Guidelines

Figure 6.7 presents a comparison between real-world GC prescribing pattern among PMR patients in primary care and the EULAR guideline recommendations over the initial 12 months of treatment. The duration of 12 months was chosen, as specific guideline recommendations were only available up to 12 months. The median monthly starting dose for the entire PMR cohort was 500mg/month (or 16.7mg/day), which corresponds well to the recommended starting dose of 375-750mg/month (or 12.5-25mg/day by the 2015 EULAR guidelines [21]. The median first GC dose was 15.0mg (IQR: 10.0-20.0mg), while the cumulative dose over two years was 3.6g (IQR: 1.8-5.1g). Patients in primary care appeared to have a much steeper tapering regimen as compared to guidelines. For example, the median monthly dose was reduced to approximately 300mg/month (or 10mg/day) in the second month of treatment, suggesting almost a 7mg taper in GC dose within 4 weeks as compared to the recommended tapering of 2.5mg/day after 4 weeks of treatment. However, the prescribed median monthly dose in month 12 appeared to be approximately 30mg/month (or 1mg/day) higher than the recommended guideline dose of 1mg/day.

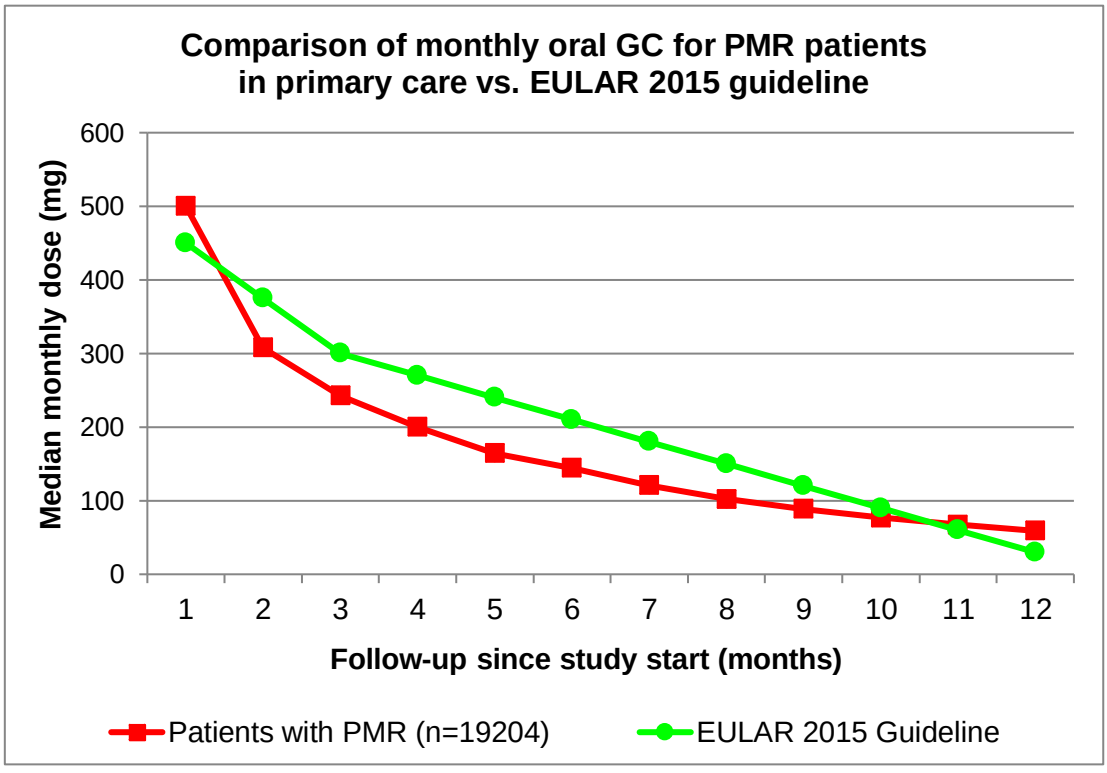


Figure 6.7: Comparison of monthly oral GC for PMR patients in primary care with EULAR guideline within the first year of diagnosis

Figure 6.8 presents a comparison real-world GC prescribing pattern among GCA (with or without PMR) patients in primary care and the EULAR guideline recommendations over the initial 12 months of treatment. Of the 3844 patients in this cohort, approximately 35% had both PMR and GCA. Of this 35% who had both diseases, 47% were diagnosed with PMR first, while another 53% had a diagnosis of GCA first. The median monthly starting dose for this cohort was 560mg (or 18.7mg/day), which was much lower than the recommended 1500mg (or 50mg/day) by the EULAR guideline [22]. The median first GC dose was 20.0mg (IQR: 15.0-35.7mg), while the cumulative dose over two years was 4.2g (IQR: 1.7-6.9g). I did some exploratory analysis by just looking at patients who had GCA as their first diagnosis. The prescribing pattern for this subset of patients did not differ from the cohort who had both GCA and a combination of both PMR and GCA, as shown in Figure 6.8. It is worth noting though, that approximately half of the initial prescriptions did not have a quantifiable dose (as shown in Figure 6.9), in which case the assumption of "one tablet per day" was applied to if no other information was available. When compared to the recommended tapering regimen by the EULAR guidelines, it appeared that GC dosing initiation in primary care for this patient population was much lower than the recommendations.

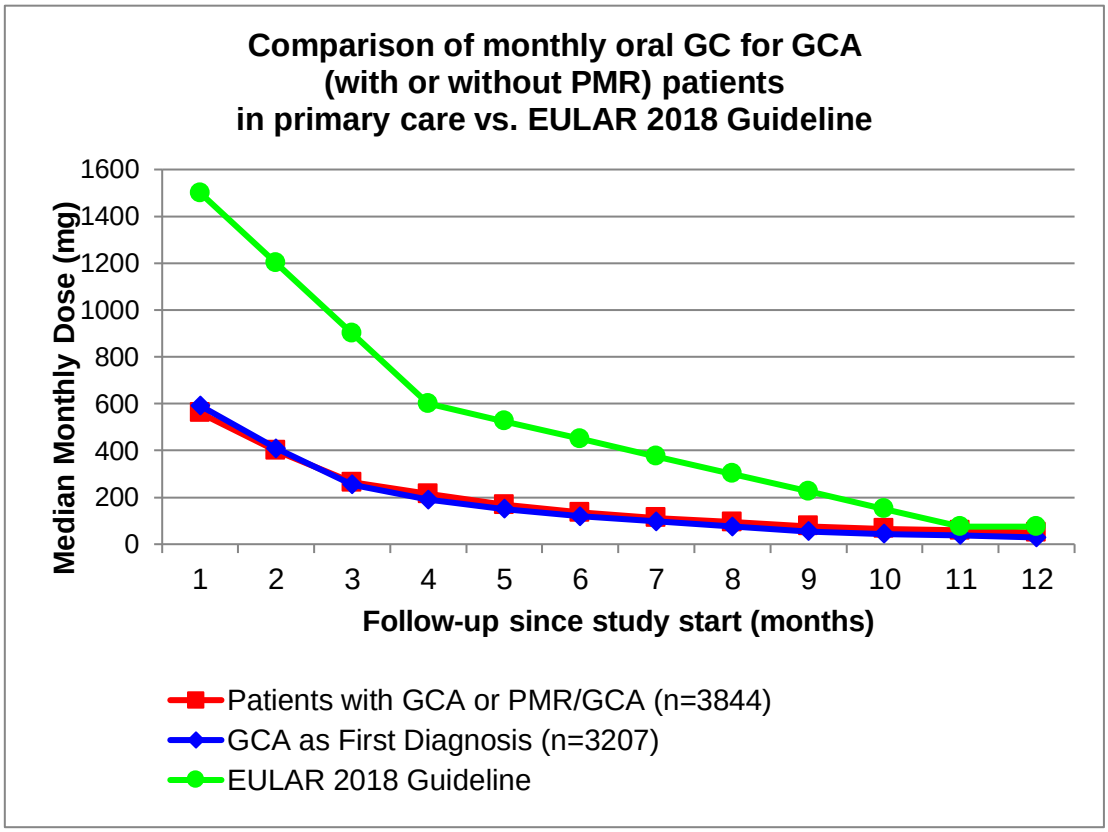


Figure 6.8: Comparison of monthly oral GC for GCA (with or without PMR) patients in primary care with EULAR guideline within the first year of diagnosis

Figure 6.9 presents the percentage of the initial oral GC prescription without a quantifiable dosing instruction among patients with GCA (with or without PMR) in primary care. As mentioned above, these were the prescriptions of which the dose and frequency were not specified; therefore the assumption of “one tablet per day” was applied if no other information was available.

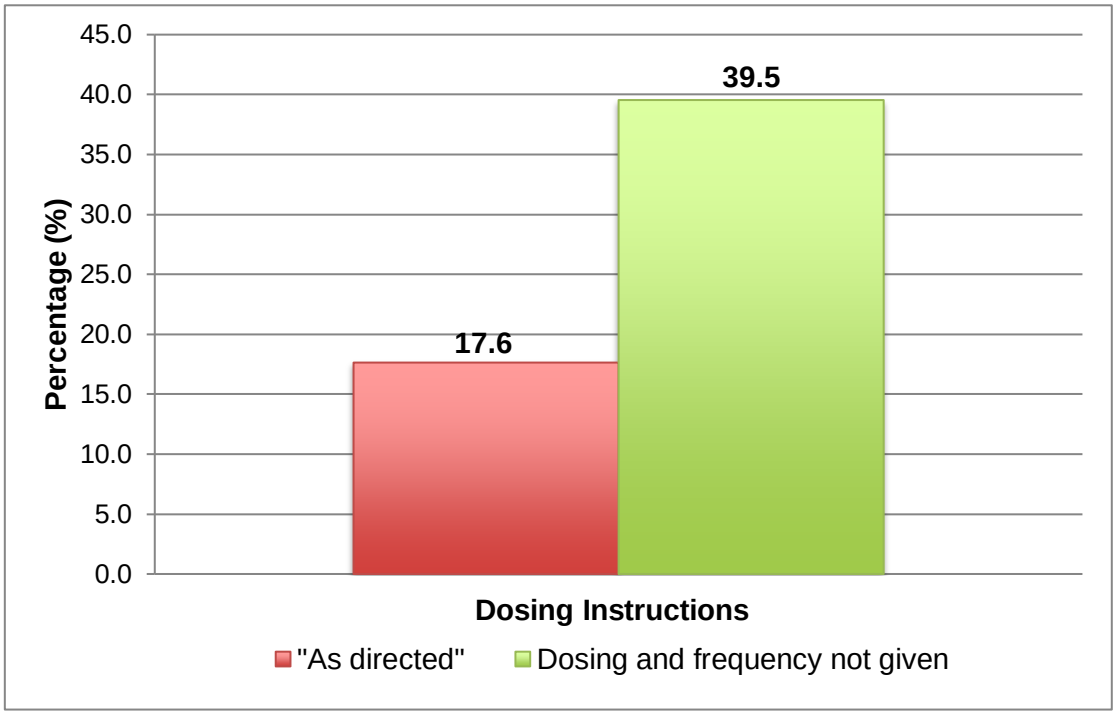


Figure 6.9: Percentage of first oral GC prescription without a quantifiable dosing instruction among patients with GCA (with or without PMR) in primary care

6.6. Pattern of Distribution for DM Over Time

This section outlines two simple descriptive frequency plots (presented as Kaplan-Meier derivatives) on the incident rate of DM over 24 months. The purpose of these plots is to have better insight on the pattern of distribution of DM over time.

Figure 6.10 presents the percentage of incident DM in PMR patients over 24 months. The results suggest that incidence of DM is highest within the first month then decreases to an approximately steady rate. Table 6.5 shows the frequency and percentage of incident DM diagnosis by month since the start of disease, with a total of 832 (4.4%) patients developing DM within the first two years of follow-up.

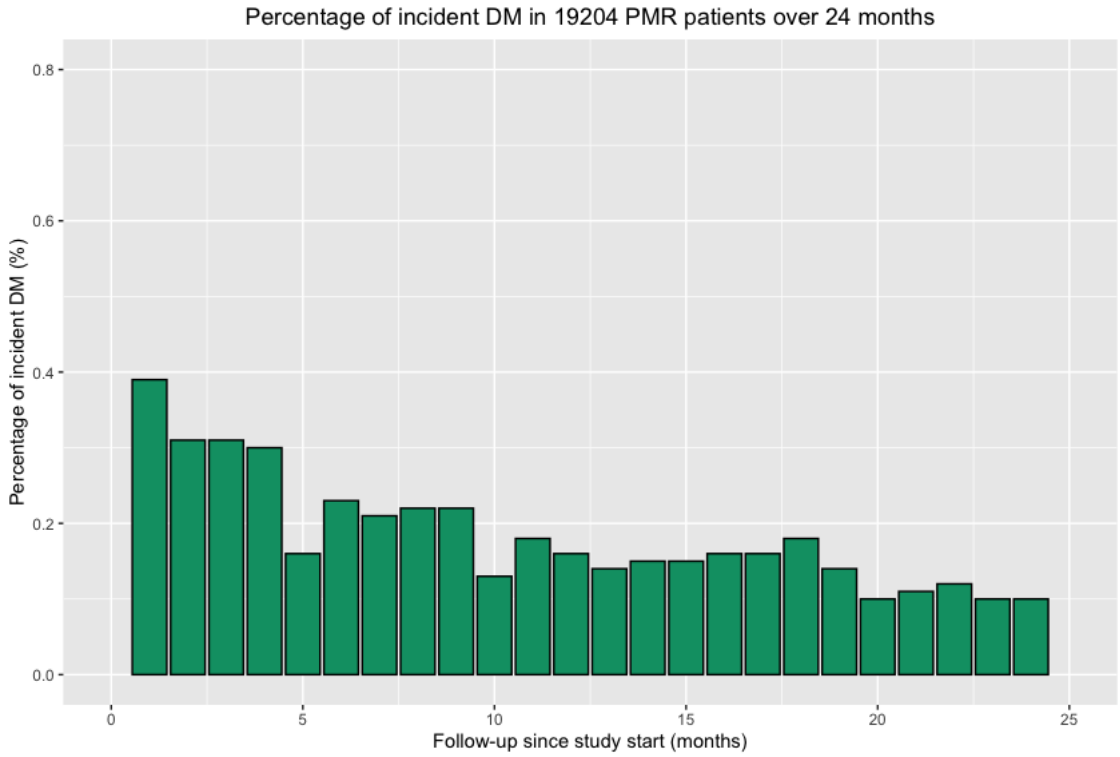


Figure 6.10: Percentage of incident DM in PMR patients over 24 months

Table 6.5: Frequency and proportion of incident DM in PMR patients over 24 months

Months	Incident DM (n)	Number at risk (n)	Percent (%)
1	75	19204	0.39
2	59	19129	0.31
3	59	19070	0.31
4	57	19011	0.30
5	31	18954	0.16
6	44	18923	0.23
7	40	18879	0.21
8	42	18839	0.22
9	42	18797	0.22
10	24	18755	0.13
11	33	18731	0.18
12	29	18698	0.16
13	26	18669	0.14
14	27	18643	0.15
15	28	18616	0.15
16	29	18588	0.16
17	30	18559	0.16
18	33	18529	0.18
19	25	18496	0.14
20	18	18471	0.10
21	20	18453	0.11
22	23	18433	0.12
23	19	18410	0.10
24	19	18391	0.10
Total	***832***		***4.43***

Figure 6.11 presents the percentage of DM in patients with GCA (with or without PMR) over 24 months. The results suggest that incidence of DM is highest within the first month, and then declines over time. Table 6.6 shows the frequency and percentage of incident DM diagnosis by month since the start of disease, with a total of 212 (5.7%) patients developing DM within the first two years of follow-up.

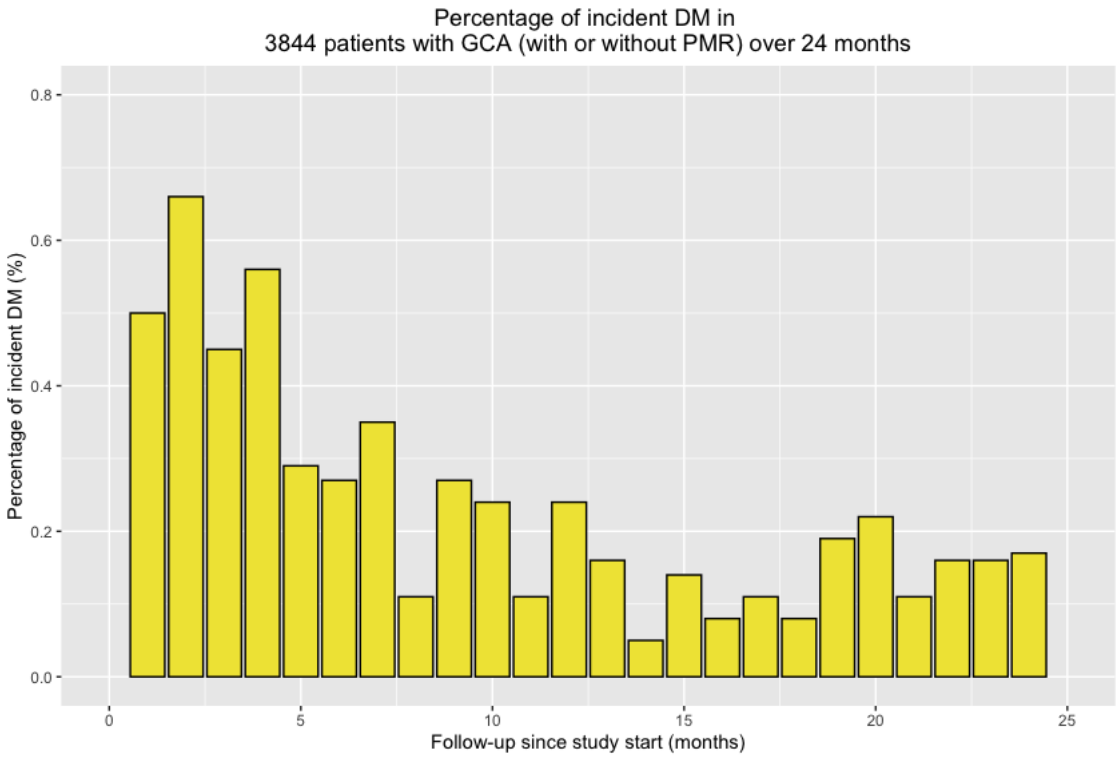


Figure 6.11: Percentage of incident DM in GCA (with or without PMR) patients over 24 months

Table 6.6: Frequency and proportion of incident DM in patients with GCA (with or without PMR) over 24 months

Months	Incident DM (n)	Number at risk (n)	Percent (%)
1	19	3844	0.50
2	25	3825	0.66
3	17	3800	0.45
4	21	3783	0.56
5	11	3762	0.29
6	10	3751	0.27
7	13	3741	0.35
8	4	3728	0.11
9	10	3724	0.27
10	9	3714	0.24
11	4	3705	0.11
12	9	3701	0.24
13	6	3692	0.16
14	2	3686	0.05
15	5	3684	0.14
16	3	3679	0.08
17	4	3676	0.11
18	3	3672	0.08
19	7	3669	0.19
20	8	3662	0.22
21	4	3654	0.11
22	6	3650	0.16
23	6	3644	0.16
24	6	3638	0.17
Total	***212***		***5.68***

6.7. Survival Analysis

6.7.1. Kaplan Meier

The results for this section are presented as Kaplan-Meier survival curves. Kaplan-Meier survival curves were used to assess time to DM diagnosis, with “event” being newly diagnosed DM. The probability of developing DM between groups was compared using the log-rank test.

6.7.1.1. DM-Free Time by Disease

Figure 6.12 presents the survival curves for time to DM diagnosis, stratified by disease group. The p-value from the log-rank test indicates that there was a significant difference in the probability of developing DM between disease groups.

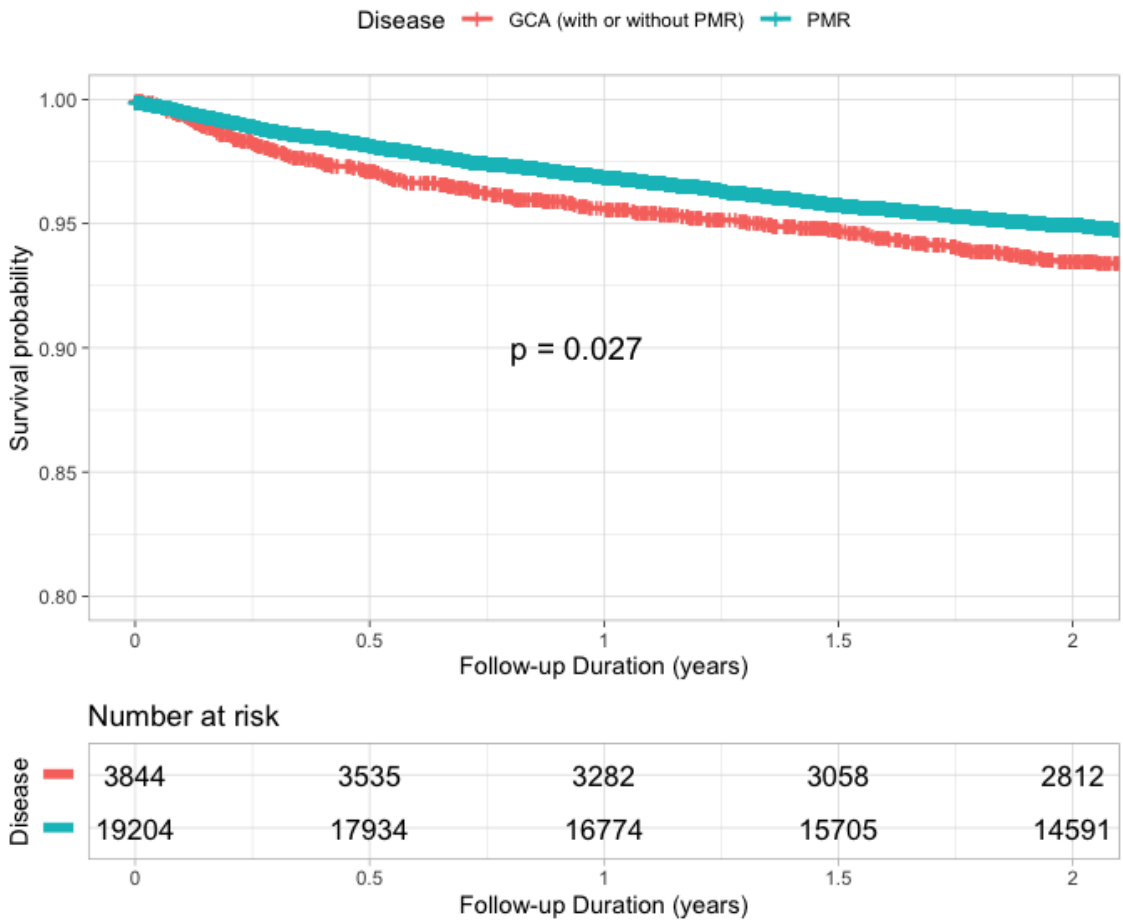


Figure 6.12: Kaplan-Meier survival curves for time to DM diagnosis, stratified by disease groups

6.7.1.2. DM-Free Time by Gender

Figure 6.13 presents the survival curves for time to DM diagnosis for males and females. The p-value from the log-rank test indicates that there was no significant difference in the probability of developing DM between genders.

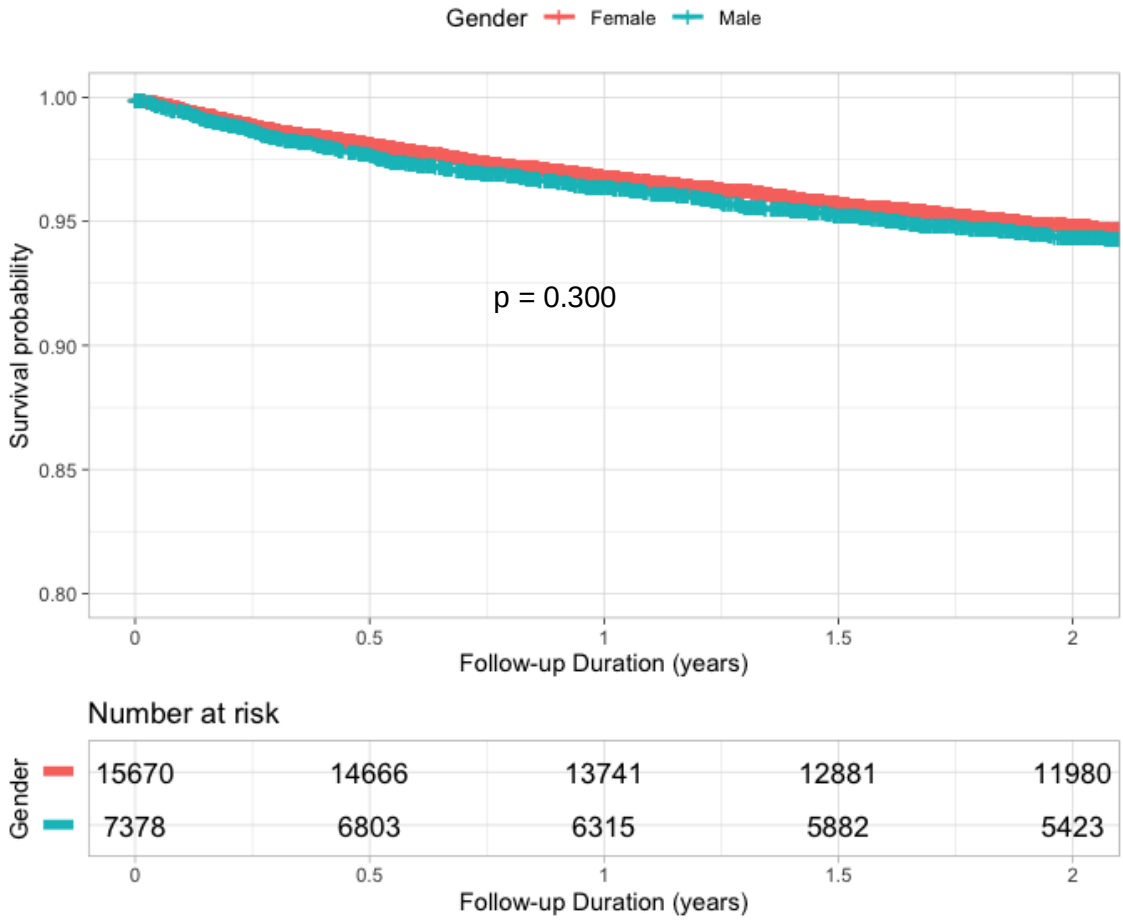


Figure 6.13: Kaplan-Meier survival curves for time to DM diagnosis, stratified by gender

6.7.1.3. DM-Free Time by Age

Figure 6.14 presents the survival curves for time to DM diagnosis by age in quartiles. The p-value from the log-rank test indicates that there is no significant difference in the risk of developing DM between age groups. The entire cohort was also divided by tertiles and quintiles for age, and Kaplan-Meier survival curves were plotted, of which there was no significant statistical difference, with p-values at 0.99 and 0.29 respectively.

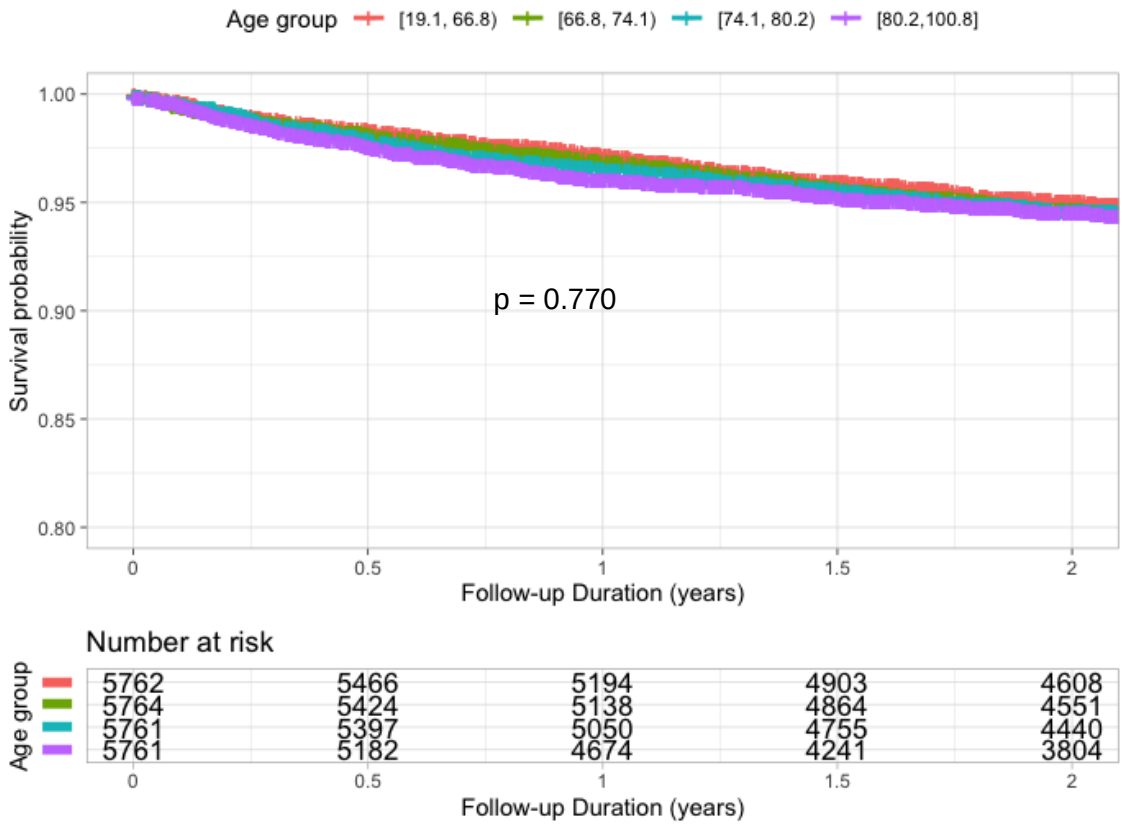


Figure 6.14: Kaplan-Meier survival curves for time to DM diagnosis, stratified by age group in quartiles

6.7.2. Extended Time-varying Cox Model

As detailed in Chapter 5, the use of the extended time-varying Cox model was a more appropriate statistical method to examine the association between GC cumulative dose and DM as it allows the incorporation of covariates that change over time into the model. For this section, I used two different approaches - firstly, the risk of DM was quantified based on each gram increase in cumulative GC dose within the initial two years of PMR/GCA diagnosis. Secondly, the risk of DM was compared between patients who were on high dose (75th percentile) versus those who were on low dose (25th percentile) within the initial two years of PMR/GCA diagnosis. The use of the "high dose versus low dose" comparison is a useful way to describe dose regimens and provides a more intuitive interpretation for clinical practice.

6.7.2.1. Extended Time-varying Cox Model for Cumulative Dose (per gram increase in risk)

Table 6.7: Extended time-varying Cox regression model for DM in PMR patients

Variables	Hazard Ratio*	95% Confidence Interval	p-value
Cumulative dose (per 10 g)	1.39	1.22, 1.60	<0.001
Cumulative dose squared (per 10 g)	1.20	1.03, 1.39	0.0184
Family history of DM	1.68	1.63, 1.74	<0.001
Non-oral GC use	1.07	1.05, 1.10	<0.001

Note: Adjusted for cumulative dose, family history of DM and non-oral GC use

Results in Table 6.7 indicate that for every 10g increase in cumulative GC dose, there was a 39% increase in DM risk while adjusting for family history of DM and non-oral GC use during study follow-up among PMR patients. The results also suggest that there was a 68% increased risk of DM in patients with a family history of DM as compared with those without; while non-oral GC use during study follow-up was associated with a 7% increase in DM risk compared to those who were not prescribed any non-oral GC.

Table 6.8: Extended time-varying Cox regression model for DM in patients with GCA (with or without PMR)

Variables	Hazard Ratio*	95% Confidence Interval	p-value
Cumulative dose (per gram)	1.02	1.02, 1.03	<0.001
Family history of DM	1.84	1.71, 1.98	<0.001
Non-oral GC use	1.30	1.24, 1.35	<0.001

Note: Adjusted for cumulative dose, family history of DM and non-oral GC use

The model in Table 6.8 indicates a 2% increase in DM risk with every gram increase in cumulative GC dose while adjusting for family history of DM and non-oral GC use during study follow-up among patients with GCA (with or without PMR). There was almost a 2-fold increased risk of DM in patients with a family history of DM compared with those without, while non-oral GC use during study follow-up was associated with a 30% increase in DM risk compared to those not prescribed non-oral GC.

6.7.2.2. Extended Time-varying Cox Model for Cumulative Dose (High dose versus low dose)

For all subsequent analyses, I will be comparing the hazard ratios between those on high dose versus those on low dose GC therapy. Patients on high GC dose were those in the upper quartile (i.e. 75^{th} percentile) and those on low GC dose were in the lower quartile (i.e. 25^{th} percentile). The difference in aggregated dose between the lower quartile and upper quartile for each month since PMR and/or GCA diagnosis was calculated, multiplied with the coefficient calculated from the extended time-varying Cox model, and then exponentiated to obtain the hazard ratio. Hazard ratios were calculated for the first 24 months since the diagnosis of PMR and/or GCA.

Table 6.9: Hazard ratios (HRs) for DM in patients with high GC dose (75th percentile) versus low GC dose (25th percentile) over 24 months using the extended time-varying Cox analysis

Months since PMR and/or GCA Diagnosis	Hazard Ratios (HRs)	
	PMR	GCA (with or without PMR)
1	1.02	1.02
2	1.03	1.04
3	1.05	1.05
4	1.06	1.06
5	1.07	1.07
6	1.09	1.08
7	1.10	1.09
8	1.11	1.10
9	1.12	1.11
10	1.13	1.11
11	1.14	1.12
12	1.15	1.12
13	1.16	1.13
14	1.17	1.13
15	1.18	1.14
16	1.19	1.14
17	1.20	1.15
18	1.20	1.15
19	1.21	1.15
20	1.22	1.16
21	1.22	1.16
22	1.23	1.16
23	1.24	1.17
24	1.24	1.17

Note: Adjusted for cumulative dose, family history of DM and non-oral GC use

Results in Table 6.9 indicate that as GC cumulative dose increases, the risk of developing DM also increases over cumulative months following the diagnosis of PMR and/or GCA. The results suggest that for PMR patients, those who were on high doses had a 2-24% increased risk of developing DM over 24 months as compared to those on low dose. The magnitude of risk was narrower in the GCA (with or without PMR) group, of which the risk ranged from 2-17% over 24 months since the start of diagnosis.

6.7.3. Rolling Cumulative Dose Model

The risk of DM from the extended time-varying Cox model is generally proportionate to the amount of cumulative GC doses over time, but as shown in Figures 6.7 and 6.8, GC doses are usually tapered over time, therefore is very likely that the risk of DM will peak at a certain time point during treatment, and then decreases. This is where determination of the timing of GC exposure is crucial. One of the methods that may be used to address this issue is the use of the rolling cumulative dose model.

Table 6.10: Concordance index of rolling cumulative dose based on months following the diagnosis of PMR and/or GCA

Rolling Months Since Diagnosis of PMR and/or GCA	Concordance Index (Standard Error)	
	PMR	GCA (with or without PMR)
1	0.555 (0.002)	0.574 (0.004)
2	*0.556 (0.002)**	*0.576 (0.004)**
3	0.555 (0.002)	0.575 (0.004)
4	0.554 (0.002)	0.574 (0.004)
5	0.553 (0.002)	0.572 (0.004)
6	0.551 (0.002)	0.570 (0.004)
7	0.550 (0.002)	0.569 (0.004)
8	0.548 (0.002)	0.568 (0.004)
9	0.547 (0.002)	0.566 (0.004)
10	0.545 (0.002)	0.565 (0.004)
11	0.544 (0.002)	0.564 (0.004)
12	0.542 (0.002)	0.563 (0.004)
13	0.541 (0.002)	0.562 (0.004)
14	0.540 (0.002)	0.561 (0.004)
15	0.539 (0.002)	0.560 (0.004)
16	0.539 (0.002)	0.560 (0.004)
17	0.538 (0.002)	0.557 (0.004)
18	0.537 (0.002)	0.555 (0.004)
19	0.537 (0.002)	0.553 (0.004)
20	0.537 (0.002)	0.551 (0.004)
21	0.536 (0.002)	0.551 (0.004)
22	0.536 (0.002)	0.551 (0.004)
23	0.536 (0.002)	0.551 (0.004)
24	0.536 (0.002)	0.551 (0.004)

* Best fitting model

Note: Adjusted for cumulative dose, family history of DM and non-oral GC use

Table 6.10 shows a comparison of the concordance index for all the models, of which the highest index was considered as the best fitting model. The results indicate that the most recent two months of GC exposure had the highest impact in both groups. The coefficients of the models in the second month for both groups were determined and applied to calculate the hazard ratios in patients with high GC dose versus low GC dose over the first two years since diagnosis, as shown in Table 6.11 below.

Table 6.11: Hazard ratios (HRs) for DM in patients with high GC dose versus low GC dose over 24 months using the rolling cumulative dose analysis

Months since PMR and/or GCA Diagnosis	Hazard Ratios (HRs)	
	PMR	GCA (with or without PMR)
1	1.22	1.34
2	1.26	1.52
3	1.37	1.55*
4	1.38*	1.48
5	1.38*	1.43
6	1.38*	1.38
7	1.37	1.34
8	1.34	1.30
9	1.32	1.27
10	1.29	1.25
11	1.27	1.23
12	1.25	1.21
13	1.24	1.20
14	1.22	1.19
15	1.21	1.17
16	1.20	1.15
17	1.19	1.14
18	1.18	1.13
19	1.17	1.12
20	1.16	1.12
21	1.15	1.11
22	1.14	1.11
23	1.13	1.10
24	1.12	1.09

*Highest DM risk

Note: Adjusted for cumulative dose, family history of DM and non-oral GC use

The hazard ratios for rolling cumulative doses over two most recent consecutive months are listed in Table 6.11. For the PMR group, DM risk was highest (38% increased risk) between four to six months after the initiation of GC therapy in patients on high GC dose as compared to those on low GC dose. The risk subsequently decreased over time. For the GCA (with or without PMR) group, the risk was highest three months after the initiation of GC therapy, as indicated by a 55% increased risk in patients on high GC dose as compared to those on low GC dose. As with the PMR group, the risk of developing DM in this group also decreased over time.

In terms of confounders, PMR patients with a family history of DM were found to have a 68% (HR: 1.68, 95%CI: 1.63-1.74) increased risk in developing DM during the most recent two months of GC exposure compared to those without a positive family history. Use of non-oral GC use during study follow-up was also associated with a 7% increased risk (HR: 1.07; 95% CI: 1.05-1.09) compared to non-users. Similarly for the GCA (with or without PMR) group, a positive family history of DM and use of non-oral GC during study follow-up were associated with an increased risk of 84% (HR: 1.84; 95% CI: 1.71-1.98) and 29% (HR: 1.29; 95% CI: 1.24-1.35) respectively.

6.7.4. Weighted Cumulative Exposure (WCE) model

While the rolling cumulative dose analysis is a useful method to determine the risk based on recent cumulative doses, it has its limitation as the time-dependent hazard is fixed for each time window. To address this limitation, I used another statistical method, namely the WCE analysis that allows cumulative dose to be calculated as a weighted mean of past doses, with higher weights assigned to more recent doses.

Table 6.12: Comparison of goodness of fit test across WCE models over 24 months

Most Recent Months To DM Diagnosis	Bayesian Information Criterion (BIC)	
	PMR	GCA (with or without PMR)
1	16211.05	3455.236
2	16183.40	3449.437
3	16120.64	3403.200
4	16105.22	3395.599
5	16097.93	***3393.847****
6	16093.24	3395.278
7	16089.28	3397.116
8	16086.20	3398.771
9	16084.40	3399.954
10	***16083.96****	3400.760
11	16084.59	3401.487
12	16085.90	3402.204
13	16087.46	3402.790
14	16088.93	3403.233
15	16090.10	3403.555
16	16090.89	3403.781
17	16091.37	3403.949
18	16091.64	3404.077
19	16091.77	3404.170
20	16091.82	3404.265
21	16091.81	3404.265
22	16091.77	3404.273
23	16091.72	3404.262
24	16091.67	3404.234

* Best fitting model

Note: Adjusted for cumulative dose, family history of DM and non-oral GC use

Table 6.12 shows the BIC results for various WCE models for the most recent months to the diagnosis of DM. For the PMR group, doses taken in the most recent 10 months had the highest impact on the risk of developing for DM; while for those with GCA (with or without PMR), the WCE weight function indicates that GC doses in the most recent 5 months to DM diagnosis had the highest impact.

Table 6.13: Hazard ratios (HRs) for DM in patients with high GC dose versus low GC dose over 24 months using the weighted cumulative dose analysis

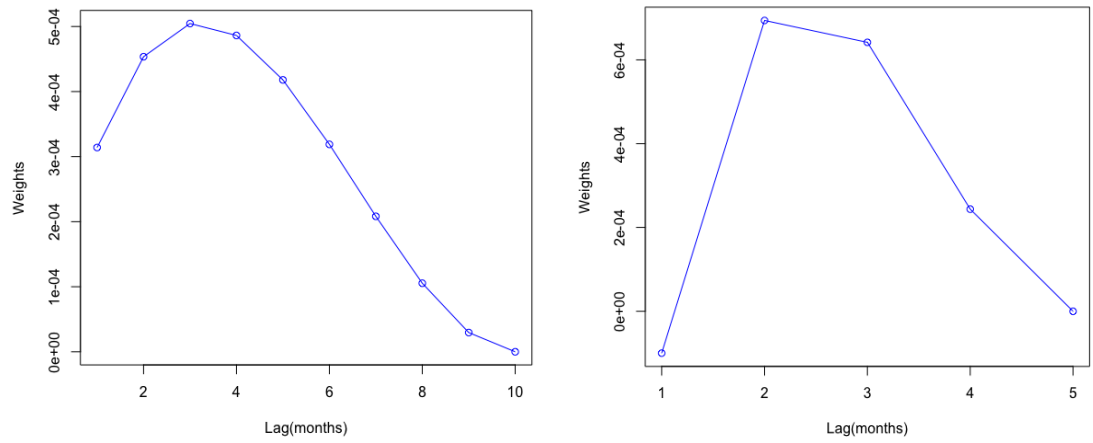
Months since PMR and/or GCA Diagnosis	Hazard Ratios (HRs)	
	PMR	GCA (with or without PMR)
1	1.15	0.91
2	1.39	1.67
3	1.69	2.73
4	2.00	2.84*
5	2.25	2.38
6	2.43	2.10
7	2.48*	1.91
8	2.43	1.77
9	2.30	1.66
10	2.16	1.58
11	2.03	1.52
12	1.92	1.46
13	1.83	1.41
14	1.75	1.38
15	1.68	1.36
16	1.62	1.32
17	1.57	1.29
18	1.53	1.26
19	1.49	1.25
20	1.46	1.22
21	1.43	1.21
22	1.40	1.20
23	1.37	1.19
24	1.34	1.17

* Best fitting model

Note: Adjusted for cumulative dose, family history of DM and non-oral GC use

To explore how the risk changes each month since the diagnosis of PMR and/or GCA, the hazard ratios were calculated and compared in patients on high GC dose versus those in the low dose group, as shown in Table 6.13. For the PMR group, the risk was highest (2.5-fold) 7 months after the diagnosis of PMR among those on a high GC dose as compared to those on a low GC dose. For the GCA (with or without PMR) group, the risk was highest (2.8-fold) 4 months after the diagnosis of GCA and/or PMR.

Figure 6.15 displays weights estimated by the best-fitting WCE models against time elapsed since GC dosing. The x-axis represents the time of which GC dose was taken, starting at month 0 until month 10 for PMR, and month 5 for those with GCA (with or without PMR). Plots indicate how the impact of past GC exposure on the development of DM decreased with increasing time elapsed since the start of follow-up. The higher weight function in the most recent time period suggests that more recent treatment has a greater impact on the risk of DM. The estimated weights across the disease groups suggested that past exposure becomes irrelevant after 10 months of GC initiation for PMR patients and 5 months for patients with GCA (with or without PMR). Interestingly, there seemed to be a delay in the onset of DM diagnosis in relation to current dose, with the highest impact only occurring at month 3 (for the PMR group) and month 2 (for the GCA (with or without PMR) group). One of the plausible reasons is that there was a delay in the recording of DM diagnosis at primary care since it would take at least two measurements of glucose test, assessment of symptoms and HbA1c testing to confirm the diagnosis of DM, for which time is needed.



PMR **GCA (with or without PMR)**

Figure 6.15: Weight functions for best-fitting WCE models of oral GC cumulative dose

In terms of confounders, PMR patients with a family history of DM were found to have a 2.3-fold increased risk of developing DM during the most recent ten months of GC exposure as compared to those without a positive family history. Use of non-oral GC was negatively associated with the risk of DM (adjusted HR=0.41). The results for the GCA (with or without PMR) group were similar. Family history was associated with a 2-fold increased risk of developing DM during the most recent five months of GC exposure, while use of non-oral GC during study follow-up was negatively associated with the risk of DM (adjusted HR=0.37).

6.7.5. Comparison of Hazard Ratios Across the Extended Time-Varying Cox, Rolling Cumulative Dose and Weighted Cumulative Dose Analyses

Figures 6.16 and 6.17 summarize the risk of developing DM between patients on high dose versus low dose over 24 months using three different statistical methods. All three methods reflect hazard ratios that indicate an increase in risk of developing DM over time, especially within the first year of follow-up. Of these three methods, results from the WCE are the most reliable, taking into account the dose, duration and recency of treatment. The result suggest that oral GC dose taken up to 10 months ago may result up to a 2.5-fold increased risk in PMR patients, while for those with GCA (with or without PMR), use of oral GC taken up to 5 months ago may increase the risk of developing DM up to 2.8-fold.

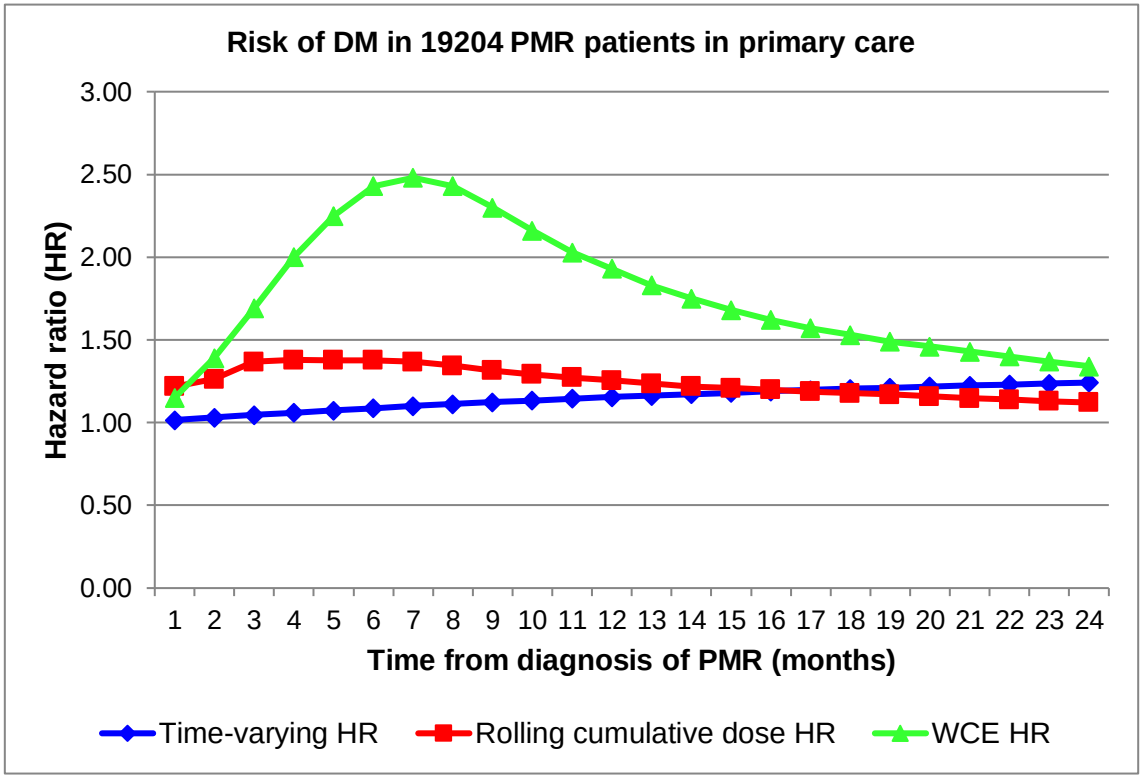


Figure 6.16: Comparison of hazard ratios across the three different statistical methods in PMR patients on high GC dose versus low GC dose

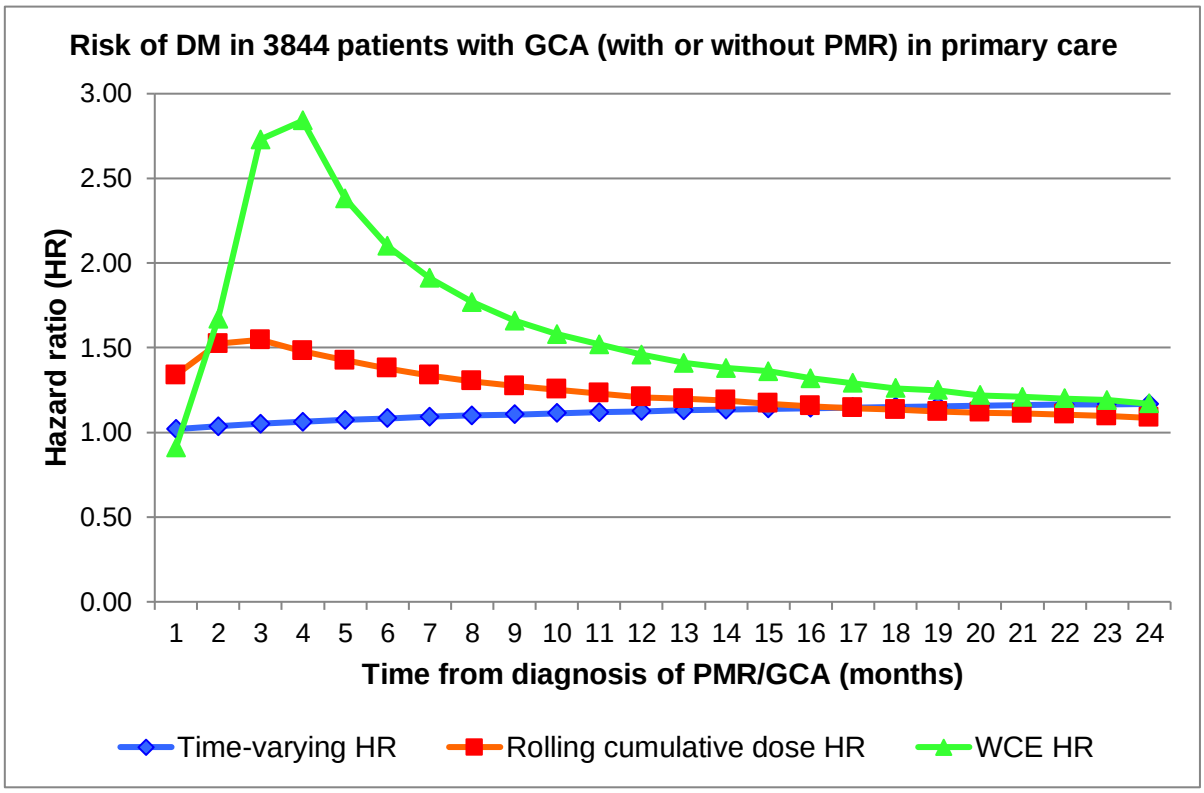


Figure 6.17: Comparison of hazard ratios across the three different statistical methods in patients with GCA (with or without PMR) on high GC dose versus low GC dose

The results for patients with PMR were more reliable as they were more likely to be treated in primary care, even in the initial stages of their disease. Patients with GCA (with or without PMR), on the other hand, were more likely to be managed by a consultant in secondary care for initial treatment before referring back to primary care for further management, therefore there is a strong possibility that GC doses captured in primary care during the initial months of treatment were largely underestimated.

In the next chapter, I will discuss the results of my findings and its impact in clinical practice.

CHAPTER 7: DISCUSSION AND CONCLUSION

7.1. Overview

This study has primarily examined the risk of diabetes mellitus (DM) associated with oral glucocorticoid (GC) use in patients with polymyalgia rheumatica (PMR) and/or giant cell arteritis (GCA) in a primary care setting. One of the issues was that all patients were exposed to GCs, therefore the risk of DM was compared between those on a high dose regimen with those on a low dose regimen. This is the first study to explore the impact of dosage, duration and timing of oral GC use on the risk of DM in PMR and GCA patients through the use of routinely collected primary care data with a large sample size using the rolling cumulative dose and weighted cumulative exposure models. All models indicated that there was a higher risk of developing DM for the higher dose regimen compared to the lower dose regimen. This is also the first study to compare trends of oral GC prescribing patterns in primary care with current clinical practice guidelines. While there have been published literatures on starting doses, average daily doses and cumulative doses, there are no published literature on the tapering regimen of oral GC doses in real-world practice as compared to guidelines. In addition, this is also the first study to compare Clinical Practice Research Datalink (CPRD) derived data (i.e. data managed by the CPRD team) with primary care data collected directly from registered primary care general practitioners to assess the completeness of CPRD derived data, which is often used by researchers in the analyses performed in many publications.

This chapter will cover the following areas: firstly, an evaluation of the results presented in Chapter 6, including a discussion on the risk of DM associated with GC use and how the study findings relate to other published literature. This sub-section will also include a discussion on GC prescribing pattern in primary care, followed by some of the challenges associated with analyzing primary care prescription databases, as well as discrepancies identified between the CPRD-derived GC data versus the original primary care data. Secondly, I will be discussing the strengths and limitations of this study, along with the appropriate steps taken to minimize the various biases. As the use of GCs in the treatment of PMR and GCA is inevitable, the third sub-section sets out considered recommendations for monitoring and treating those who actually develop DM after GC treatment. This chapter will end with an outline of future work and a summary of the thesis.

7.2. Evaluation of Study Findings

7.2.1. Risk of DM associated with Oral GC Cumulative Dose

There have been published literatures exploring the association between oral cumulative GC therapy and DM risk in patients with PMR and/or GCA patients, and while these studies explored the impact of dosage and duration of GC use on risk of DM, none of them considered the recency of GC exposure. It is insufficient to only consider the time-dependent aspect of GC exposure, as recency of exposure might be just as crucial. For my PhD, I used three different statistical methods, including the extended time-varying Cox model, the rolling cumulative dose model and weighted cumulative exposure (WCE) model, to quantify the risk of DM associated with oral cumulative GC use. Of the three methods used, the novel rolling cumulative dose and WCE models have added insights into the dose and temporal relationship between oral cumulative GC use in primary care and risk of developing DM in patients with PMR and/or GCA. The WCE model depicts the use of GCs in clinical practice best as it allows GC exposure to be represented as the weighted sum of past doses, allowing the most recent doses to be given the most weight using cubic splines.

7.2.1.1. Risk of DM associated with Oral GC Cumulative Dose in PMR Patients

Results from the rolling cumulative dose and WCE analysis suggest that PMR patients on high dose GC therapy have up to 1.4-2.5-fold increase in DM risk compared to those who were on low dose therapy. A typical high GC dose (75^{th} percentile) in the initial month of treatment was 24mg/day and a typical low dose (25^{th} percentile) was 9mg/day in my dataset of PMR patients, following which doses were tapered down over time. To date, there are relatively very few publications on the incidence of DM in patients with PMR compared to patients with GCA. Results from my meta-analysis in Chapter 4 showed that the incidence of DM associated with GC use was only reported by 9 studies up till 2017, all of which had small sample sizes of less than 250 patients. The incidence proportion of GC-induced DM based on these studies was 6%, which was 1.2% higher compared to the UK general population of similar gender and age group [11]. A more recent study from an academic medical centre in North America mainly consisting of northern European ancestry PMR patients reported that there was no difference in the rate of GC-induced DM as compared to their age and sex-matched comparators without PMR [298]. The sample size for that study was however, relatively small (359 patients) as compared to my current study (19,204 patients).

Results from the WCE analysis also indicated that the risk of developing DM was only significant within the most recent ten months of treatment, with the highest risk being at month seven. Results from the rolling cumulative dose support this finding, with the highest risk occurring between four to six months after GC initiation. One of the unique findings of this study is that the GC effect on DM lasts for several months but becomes negligible (diminishes to almost zero) after approximately one year.

7.2.1.2. Risk of DM associated with Oral GC Cumulative Dose in Patients with GCA (with or without PMR)

Results pertaining to the risk of DM associated with oral GC cumulative dose in patients with GCA (with or without PMR) ought to be interpreted with caution, as it is very likely that the initial doses of GC therapy in this study are an underestimate of what is actually being prescribed in a real-world setting. This is because GCA patients are often initially managed in secondary care as the disease itself is considered to be a medical emergency [299, 31], of which untreated cases may lead to permanent blindness; thus early and rapid treatment with high GC doses is believed to be crucial to control inflammatory symptoms and prevent ischaemic manifestations. Since CPRD is a primary care database, any initial (likely higher) doses of GCs prescribed in secondary care were not available. As a result, it is likely that the risk of DM is underestimated. There is however, a small possibility that the risk might be overestimated because patients may have had a relatively low oral GC dose but a large non-oral GC dose. Since “non-oral GCs” was adjusted as a binary variable, the actual magnitude of DM risk may have been disrupted. This is however, unlikely, as most non-oral GCs are unlikely to be given long term (i.e. intravenous GCs are usually only given in the initial stages of treatment of GCA for less than a week). Another factor to consider is the bioavailability of the drug, which is often dependent on the mode of administration. Systemic GCs given intravenously will have a 100% bioavailability, but as mentioned, they are usually only given for a short duration, therefore unlikely to have a large impact on the estimation of DM risk. Another type of non-oral GC that may have been commonly used in this group of elderly patients is inhaled GCs for the treatment of respiratory diseases such as asthma. Inhaled GCs have a very low bioavailability (16-28%) [300]; therefore it is unlikely that the use of inhaled GCs would result in a higher DM risk even if given for a long duration. This hypothesis is supported by one large nested case-control population study in the UK, of which the authors reported that non-oral GCs (including inhalers, topical preparations, eye drops and injections), had no association with the development of incident DM [181]. An issue of interest is whether the addition of these non-oral GCs (especially the high dose

systemic GCs with excellent bioavailability) actually alters the magnitude of DM risk when given concurrently with oral GCs. This is however, beyond the scope of this PhD, as prescribed medications in secondary care were not linked to CPRD. Despite this limitation, results from my analyses still showed an increased risk of DM by up to 1.6-2.8-fold in patients on high GC dose versus low GC dose. A typical high dose (75^{th} percentile) and low dose (25^{th} percentile) in the initial month of treatment for this patient population was 35mg/day and 7mg/day respectively.

I was unable to do a direct comparison with other studies as the methods used to quantify DM risk associated with cumulative GC dose varied across studies. The pattern however, was consistent with published literatures that looked at the effect of oral cumulative GC dose on DM risk. One large nested case-control study reported that newly diagnosed GCA patients exposed to prednisolone 30mg/day had almost a 5-fold increased risk (Adjusted OR=4.7; 95%CI: 2.8-7.8) of developing DM compared to those with a low average daily prednisolone dose of 5mg/day [281]. The study also reported a trend of increasing risk with increasing cumulative prednisolone dose, with a 2-fold increased risk of DM observed in the highest cumulative dose category (≥20g) compared to the lowest dose category (≤3g) [281]. One population-controlled Danish study looking at 1849 vasculitis patients, of which 91% of the patients were diagnosed with first-time GCA, reported that median cumulative prednisolone-equivalent dose (PED) dose of ≥5.6 grams was associated with a hazard ratio for DM of 1.6 (95% CI: 1.02-2.5), and a 30% increased DM risk per 10mg increase in average daily oral prednisolone equivalent dose (HR: 1.3; 95% CI: 1.01-1.80), all within the first year [245]. Another CPRD cohort study also reported that newly diagnosed GCA patients had a 1.4-fold increased risk of developing DM compared with non-vasculitis patients, though the authors did not report any information on the total cumulative dose or duration of GC use in this patient population [258].

One retrospective cohort study using US claims data reported that the risk of new-onset DM rose by 5% (HR=1.05; 96%CI: 1.03-1.07) with each gram of oral GC exposure in patients with newly diagnosed GCA [264]. Results from the extended time-varying Cox regression model in my study indicated a 2% (HR=1.02; 95%CI: 1.02-1.03) increase in DM risk with each gram of oral GC exposure in these patients. It is important to note though, that the authors in this study had full access to all GC prescriptions from the claims data, as indicated by the median initial oral GC dose of 40mg/day; while the median initial oral GC dose in my study was only 20mg/day.

Results from my WCE analysis suggest that oral GC dose taken in the most recent five months of treatment had a significant impact on DM risk, with the highest impact being at month four. The rolling cumulative dose model also showed a similar pattern, with the highest impact of DM risk being at month three. This pattern is consistent with other published studies for GCA patients. One large nested case-control study reported that majority of DM cases associated with GC use occurred within 2 years following initiation, with over 40% of DM cases developing during the first year [281]. Another Danish study reported that the incidence risk ratio of new-onset DM was 7.0 (95% CI: 5.2-9.3) in their GCA cohort during the first year of observation when compared to the general population. Beyond the first year, they reported that the incidence rates for DM were not significantly increased [245]. In another large observational study of 5,011 GCA patients, the incidence risk ratio of DM was 1.4 (95% CI: 1.2-1.7) as compared to matched non-GCA patients [263], of which the median time for the occurrence of DM in the GCA group was one year from the start of treatment. While all these published literatures support the hypothesis that the risk of developing DM is highest within the first year of GC use, my study findings have added on insights on the specific timing when the risk is highest, which is likely to be within the first six months of therapy initiation.

Among the confounders considered, family history of DM was associated with nearly a 2-fold higher DM risk across groups when adjusting for cumulative dose and non-oral GC use during follow-up using the extended time-varying Cox regression, rolling cumulative and WCE models. The result is consistent with published studies that examined the association between family history of diabetes with type 2 DM, of which it was reported that those with a first-degree relative having DM had a more than two-fold excess risk [301-304], especially among those of European ancestry [305]. Results for non-oral GC use during study follow-up were inconclusive from my study. The extended time-varying Cox model and rolling cumulative model suggested an increase in risk: 7% for PMR patients and 30% for patients with GCA (with or without PMR), but the WCE model suggested a negative association (HR: 0.41 & 0.37) for the PMR group, and GCA (with or without PMR) group respectively. One of the possible reasons for this discrepancy is related to the recency of oral GC exposure. The hazard ratios for the rolling cumulative model was calculated based on the coefficient of two most recent consecutive months since diagnosis for both groups, while the WCE model was calculated based on the most recent 10 months for PMR and 5 months for GCA (with or without PMR). There is a possibility that the risk is higher in the initial months since PMR/GCA diagnosis, when given concurrently with higher oral GC doses but declines over time. This however, was not explored in detail, as use of non-oral GC during study

follow-up was only accounted for as a binary (yes/no) variable in my study. Non-oral GCs (including inhalers, topical preparations, eye drops and injections), as stand-alone prescriptions, have been reported to have no association with the development of incident DM in one large nested case-control population study in the UK, but the authors did not evaluate the risk of DM association with these treatments when given concurrently with oral GC therapy [181].

One issue of interest from the results (Table 6.1 in the results chapter) was that PMR appeared to have a lower prevalence in the most deprived index of multiple deprivation (IMD) quartile (quartile 4), but similarly common across the first three quartiles. This is an indicator that PMR may be under-represented in the quarter of the population living in areas with greater levels of socio-economic deprivation. One of the possible reasons is that PMR patients in my study population were incident cases; therefore it is possible that those with better socio-economic status (SES) were presented to their general practitioners (GPs) in the initial stages of their disease because of better access to health care and better health awareness. People in the community with lower SES have been reported to have poorer physical and mental health and poorer access to health care [306]. One study investigating the association of PMR with SES in primary care reported that no association was found between PMR and SES [307]. This study however, included all PMR patients (not just incident cases), and involved only eight GPs in North Staffordshire. Since there were only eight practices included, there may not have been a sufficient range of SES for the effect to be apparent. Therefore, the results from that study may not apply to my study population.

7.2.2. GC Prescribing Pattern in Primary Care

Relatively little is known about real-world oral GC prescribing patterns of PMR and/or GCA in primary care. While there have been a few surveys and studies reporting the starting dose, average daily dose, cumulative dose and duration of GC use, none of these studies described the pattern of GC use over time.

7.2.2.1. GC Prescribing Pattern in PMR Patients

PMR patients are usually diagnosed and managed in primary care if there are no complications. One study consisting of 183 PMR patients in the UK reported that 83% of these patients were managed exclusively in primary care without reference to specialist opinion [308]. Another recent survey of UK GPs reported that of the 1249 respondents, only 6.4% (n=80) would refer all PMR patients to secondary care as a matter of routine care [309]. These studies support the idea that in the UK, PMR patients are generally managed in primary care; which was also reflected in my study findings as the prescribing pattern of oral GC corresponded fairly well to the 2015 European League Against Rheumatism (EULAR) guidelines suggesting that GC was mostly initiated in primary care for these patients [22].

The median monthly oral starting GC dose for PMR patients in my study was 500mg/month (or 16.7mg/day), which corresponds well to the recommended starting dose of 12.5 - 25mg/day by the 2015 EULAR guidelines [21]. The median first GC dose was 15.0mg (IQR: 10.0-20.0mg), which was in agreement with another CPRD study that also reported a median first GC dose of 15.0mg (IQR: 8.0-21.0mg) [12]. Helliwell et al, in their qualitative study exploring the management of PMR among UK GPs, reported that 56.4% (n=704) of study respondents would initially treat PMR with either 15mg or 20mg of prednisolone [310]. Their survey finding was consistent with the results from my study.

The median average daily dose of GC prescribed for the entire follow-up duration in the practice was 6.6mg/day (IQR: 5.0-9.6mg/day); while the total cumulative dose for the entire follow-up duration in the practice of approximately 4.5 years was 4.1g (IQR: 2.0-7.6g). These findings were similar to the above-mentioned CPRD study of incident PMR patients, of which the authors reported a median average daily dose of 6.0mg (IQR: 4.0-9.0mg) and a median total dose of 4.0g (IQR: 2.0-8.0g) [12]. In addition, I also looked at the cumulative dose for the first two years of follow-up. The cumulative dose over two years was 3.6g (IQR: 1.8-5.1g), which was approximately 88% of the

total cumulative dose for the entire follow-up duration in the practice, suggesting that the extent of GC use was highest within the first two years of follow-up. The median duration of treatment in my study population was approximately 1.7 years (IQR: 0.7-3.5 years). The above-mentioned CPRD study also reported similar findings, with the median duration for total GC treatment time of 1.9 years (IQR 1.0-4.0 years) [12], while another study that looked at PMR patients in three UK GPs reported a median treatment duration of 1.4 years (IQR: 0.8-2.4 years) [308].

When compared to the 2015 EULAR guidelines, patients in primary care appeared to have a much steeper tapering regimen. GC doses were halved to approximately 8.1mg/day (from the initial 16.7mg/day) after merely three months of treatment. GC doses were tapered off rapidly until the ninth month, of which doses were then tapered more slowly than the EULAR guidelines suggest. This slower tapering pattern at the end of the first year may be due to a few reasons. Firstly, it is possible that those were the minimum effective doses to keep patients in disease remission, and that the dose was held at a particular level for a subset of patients in order to keep their symptoms under control. Secondly, patients or clinicians may have been reluctant to stop the treatment for fear that symptoms may restart, and while they may be concerned with adverse events associated with high GC dose, they may have the perception that the risk of adverse events associated with low GC dose is very low. Therefore, they are not in a hurry to stop treatment beyond a certain level of low GC dose. Thirdly, it is also possible that some of these patients eventually developed a relapse or flare in disease, requiring a significant dose increase. At the group level this would increase the average monthly dose. A few studies reported that the relapse rates were associated with higher initial GC dose and faster GC tapering rates [311, 312]. Because of the concern of over-rapid tapering of GC doses leading to increase in relapses, Kirwan et al suggested a new regimen that minimizes the risk of relapse. They recommended a starting dose of 15mg daily for six weeks then 12.5mg daily for six weeks, then a 10mg maintenance dose for one year, with a 1mg/per month taper thereafter if needed [313]. The authors also reported a 20% lower rate of relapse at two years using this new regimen, as compared to another cohort that used a more rapid dose reduction regimen in line with current British Society for Rheumatology (BSR) recommendations [233]. The issue of how GCs should be tapered in the safest and most effective way with minimal relapses however cannot be determined in this study and is beyond the scope of this PhD.

7.2.2.2. GC Prescribing Pattern in Patients with GCA (with or without PMR)

GCA patients, on the other hand, are more likely to be managed in secondary care in the initial stages of their disease, as they are usually referred for specialist review and diagnostic confirmation, as recommended by guideline [7]. Though the actual rate of referral is unknown, one survey showed that 35.6% of 1251 UK GPs would refer patients with suspected GCA to secondary care without initiating GCs [309]. The response of this survey seemed to reflect my study findings – of which 39.5% of first oral GC prescription did not have any information on dosing and frequency, suggesting that these patients may have been managed in secondary care. The survey also reported that 49.7% would initiate GCs before referring the patients out to secondary care, of which the most common initiating dose was 60mg of prednisolone [309]. One of the potential challenges with this group of patients is that, the first GC prescription may be available in primary care, but subsequent prescriptions will not be available, as they will be seen in secondary care. The first prescriptions for these patients are also likely to be shorter in duration, as the main purpose of these prescriptions was to keep their symptoms under control while waiting to be seen by specialists in secondary care. It is therefore not surprising that the prescribing pattern among patients with GCA (with or without PMR) seemed to be much lower than recommended guideline doses in my study. The median monthly starting dose was 560mg/month (or 18.7mg/day), and the median first GC dose was 20.0mg (IQR: 15.0-35.7mg) in my study. The results are consistent with another study that looked at a subgroup of UK patients in primary care, of which the authors reported a median GC starting daily dose of 20mg/day (IQR: 10-40mg/day) [314]. The median average daily dose of GC prescribed for the entire follow-up duration in the practice was 9.8mg/day (IQR: 6.5-17.3mg/day); while the median cumulative dose for the entire follow-up in the GP practices duration of approximately 4.4 years was 5.3g (IQR: 2.0-7.6g). The median cumulative dose from my study was comparable to another CPRD study involving only incident cases of GCA, of which the authors reported a median cumulative dose of 5.1g for patients up to more than two years of follow-up [77].

The cumulative dose over two years was 4.2g (IQR: 1.7-6.9g), which was approximately 79% of the total cumulative dose over the entire follow-up duration in the practice, suggesting that the extent of GC use was highest within the first two years of follow-up, as with the PMR group. The median duration of treatment in my study population was approximately 1.5 years (IQR: 0.4-3.5 years).

When compared to the 2018 EULAR guidelines, patients in primary care appeared to have a much lower treatment regimen, though the results do indicate a tapering trend over time in accordance with the guidelines. In my study, 57.1% of first oral GC prescriptions did not have a quantifiable dosing instruction, for these prescriptions, the assumption of “one tablet per day” was applied if no other information was available. This would have resulted in a substantial underestimation in dose as nearly two-thirds of the prescriptions were 1mg and 5mg prednisolone tablets, whereas the expected initial dose would be between 40-60mg. Another important observation is that since patients were unlikely to be prescribed with 1mg or 5mg tablets if they were to be on high dose GCs (i.e. 40-60mg), therefore there is a possibility that the “first” oral GC prescription recorded in CPRD may not truly be the “first” prescription, but more likely to be the “first prescription upon discharged from secondary care”.

7.2.3. Challenges Associated With Primary Care Prescription Databases

There were many challenges associated with data cleaning and analyzing complex primary care prescription databases such as CPRD; and while some were related to the complexity and variability in abbreviations or prescribing terminologies, some were simply related to transcribing errors such as misspellings. I have summarized here some of the major challenges encountered during the database cleaning process:

7.2.3.1. Misspellings

It was fairly common to come across misspellings in the free text section of the prescription database, as with other types of clinical text [315, 316]. Most of them were typos. Some of the misspellings were insertions of unnecessary alphabets, such as “1 ddaily” or “1 daily6” or “1 dailly”, and some were deletions of alphabets such as “1 dail“ or “1 dail;”, while some others were merely straightforward typos such as “as directde” or “as direced” etc. There were also examples where the spacing between words was omitted, such as “1aday” instead of “1 a day”. Most of these misspellings were either keywords of dosing or frequency, e.g. “1 mnae” instead of “1 mane”; or “notce” instead of “nocte” which was a challenge when using computer-coding system, as the system failed to recognize the misspelled keyword, resulting in that particular prescription being excluded or miscategorized. Another major misspelling issue was associated with the letter “O” and the number “0”. There were multiple prescriptions in the database where “OM” was written as “0M”, of which it was unrecognized by the computer coding system. To address this issue, manual screening was done to appropriately extract relevant prescribing data. The complexity of this problem is

reflected in the instruction “as directed”, as there were 44 different typos and misspellings for this one specific instruction.

7.2.3.2. Ambiguity in interpretation

There were multiple cases where the prescription text may be interpreted in more than one way; and to address this problem, clinical judgment played a crucial role. For example, a prescription of “3 per day” may be interpreted as either 3 tablets taken once, or 1 tablet taken 3 times. Since GCs tend to be taken in a single daily dose, therefore the first intuition would be to consider it as 3 tablets taken once. In this case, the pattern of administration within a day may not be important for data analyses, as the goal was to look at the average dose per day and cumulative dose; therefore in this case, it did not matter which assumption was used to extract the information. There were, however cases where the assumption mattered as different interpretations would result in major differences for the cumulative dose and average dose per day. One typical example is a prescription of “1/2 alt days”. This may be interpreted as “1, then 2 tablets taken alternately each day” or “half a tablet taken on alternate days”. The interpretation of the prescription in this case would make a huge difference (1.5 tablets per day versus only 0.25 tablets per day). The first intuition was to assume that the first assumption of “1, then 2 tablets taken alternately each day” to be more likely, as it would make more sense for the prescriber to write “0.5 EOD” instead of “1/2 alt days” if the patient were really meant to take “half a tablet on alternate days”. There were also similar prescription styles of “2/1 alt days’ and “2/3 alt days” etc, of which the first assumption would again makes more clinical sense, as it would not make sense to write “2/1” instead of “2”. In addition, it would not make sense to request patients to divide tiny prednisolone tablets into 3 portions, and to take 2 of the 3 portions on alternate days. To further confirm that the first assumption was more likely of the two, 5 random sets of the “quantity of tablets prescribed” were selected and the total duration of treatment was calculated (by dividing the “quantity of tablets prescribed” with “number of tablets per day”) and compared with the dates of the next consecutive visit. For example, if the prescription was “1/2 alt days” and the patient was prescribed with 84 tablets; then the 2 possibilities would be either 84/1.5 = 56 days or 84/0.25 = 336 days. This would then be compared with the dates of the next consecutive visit for the patient, and if the next scheduled appointment was to be 2 months later, then this would correlate with the first assumption. All 5 random samples supported the first assumption, therefore it was concluded that the interpretation of this prescription style would be to take “x, then y number of tablets alternately each day” unless specified otherwise.

7.2.3.3. Varying dosages and tapering regimens

Another major challenge was the variation in prescribing patterns, especially for cases where medications required administration at different specific time, e.g. “take one tablet at 10am” or “take one at teatime”. The specificity of these instructions resulted in this type of prescription not being captured by the computer coding system, therefore, the only option was to manually screen for them. There were also some prescriptions that required tapering in doses, which was also difficult to capture using the computer coding system, as the doses and dosing frequency were not fixed.

7.2.3.4. Non-specific instructions

As discussed in the results chapter, approximately half of the prescriptions had a “as directed” or no GC dosing instructions. Each GP has a practice formulary with a clinical drug database to facilitate electronic prescribing. For most medications with a fixed dosing regimen (e.g. anti-hypertensive medications, anti-diabetic medications or antibiotics), a default instruction is usually pre-set to minimize prescribing errors. These default instructions can be changed by the prescriber if patients were to take the medication differently to the default. The challenge with treatment regimens that require tapering such as GCs is that there is no fixed dosing regimen, therefore the default instruction in the clinical drug database is often written, “as directed”. GPs are encouraged to change these “as directed” prescriptions into specific instructions, but this remains a challenge for the following reasons. Firstly, the dose may have been specified by a hospital consultant if the patients is under secondary care, so more often than not, patients are told to adjust their medication as directed by the specialist. Therefore the “as directed” may mean “reduce the dose by 1mg if blood test is normal” and the patient is expected to make the necessary adjustment once the result is known; or in other cases, the “as directed” may refer to “reduce the dose by 1mg if the pain is gone or when symptoms have resolved”. Secondly, when a prescription is reissued, the easiest and fastest way for a prescriber to do so is by clicking on the previous prescription for that patient and enter reissue. Although the prescriber may change the instructions if needed, it is often presumed that the patient will continue taking the way they have been previously been instructed on. Thirdly, there is a possibility that GPs record the instructions as “free text” in the clinical notes (which is not accessible to researchers), and instructed the patient verbally on the specified dosing instructions; and with GCs being one of the most common medication that requires tapering, the pharmacist may not query the GP on specific instructions upon receiving the prescription.

Data cleaning of the prescription database will remain a challenge because of its size and complexity. Not only does it require adequate computer hardware and software, it also requires experience in data management and expertise in computer programming with clinical input. An effective data cleaning approach that fulfils the following requirements would be helpful to promote efficiency and minimize errors [317]: firstly, it should be able to detect and remove all major errors and inconsistencies, especially during the integration of multiple sources. Secondly, the approach should be supported by tools that require minimal manual inspection and programming effort. Thirdly, the algorithm for data cleaning should be specified in a declarative way and be usable across the various disease domains as well as for query processing. One potential solution is the incorporation of an automatic misspelling detection and correction system with the rule-based natural language processing (NLP) method. While rule-based approaches may also be implemented using statistical softwares such as R or Stata, they are only applicable if the extent of misspellings and typos is already known. This is however, a challenge, as the range of possibilities for any misspelling and typo errors are unknown unless screened manually, as discussed above. One study that applied their spell checker to three different types of free-text data: clinical notes, allergy entries and medication orders reported a detection performance of up to 94.4% and correction accuracy of up to 88.2% [315]. Another study incorporated a few spell-checking algorithms for NLP in vaccine safety and reported a sensitivity of 74% and specificity of 100% [318]. The following spell-checking algorithms were proposed in their study: firstly, the “metaphone” algorithm which was used to search for similar sounding words. Secondly, the “header” algorithm that looked for words with the same first four characters. Thirdly, the “N-gram” algorithm that allowed mid-string searches. Fourthly, the “transposition” algorithm that search for words where any two characters are switched. Fifthly, the “deletion” algorithm that search for word matches by sequentially inserting a wildcard character in the misspelled word to simulate a character deletion. Next, the “insertion” algorithm that searched for word matches by sequentially deleting a character in the misspelled word to simulate a character insertion, and lastly the “substitution” algorithm that searched for word matches by simulating character substitution. Results from these studies showed promising results, but it will still be some years before the use of automated misspellings checkers in NLP can fully be implemented in primary care research due to strict governance and access restrictions on the use of free text.

7.2.4. Comparison Between CPRD-derived Data and Primary Care Data

There were 2 discrepancies found between CPRD-derived data and the data I extracted from primary care for the “number of tablets per day” variable. Information for this variable was mainly extracted from the “dosage instructions” variable, and any instructions that involved “X mg” (e.g. 40mg daily) was coded as X number of tablet (e.g. 40 tablets) in the CPRD-derived data, without taking into consideration the tablet strength. In this example, the total number of tablets should have been 8, after taking into consideration that it was a 5mg prednisolone tablet, and not 40. This misclassification would have led to an overestimation of the daily dose, as the number of tablets per day will eventually be multiplied with the tablet strength and PED to obtain the final daily dose. The other discrepancy was related to prescriptions that involved “alternate days” dosing (e.g. 1/2 alt days”). This may be interpreted as “1, then 2 tablets taken alternately each day” or “half a tablet taken on alternate days”, of which the CPRD-derived data opted for the latter. Both interpretations are plausible, but the first interpretation was clinically more likely. Details on how these instructions were interpreted in this study have been presented in Section 7.2.3.2. While the first type of misclassification would have resulted in an overestimation of the daily dose, this type of misclassification would have resulted in an underestimation of the daily dose for the CPRD-derived data, and the balancing out of these two effects might make any errors in the calculation of daily dose harder to spot in the group-level data.

Another problem with the CPRD-derived data was inconsistency in the application of the assumption of “once per day” dosing if no specific instruction was given. The assumption was only applied in some cases and there was no clear pattern on the criteria of which the assumption was applied to. Since the CPRD-derived prescription data was mostly managed using pre-defined computer algorithms and dictionaries with minimum human manual screening, it is likely that misspellings may have contributed to this inconsistency especially given that misspelling errors were common in the prescription database, as discussed in section 7.2.3.1.

While a few discrepancies have been identified between CPRD-derived data and the data I extracted from primary care, they are unlikely to have any significant impact on the analyses. Even if there were to be some misclassifications in the number of tablets (e.g. 40 tablets instead of 8 of the 5mg tablets), most researchers would eventually apply a cap in the maximum daily dose based on clinical judgment; therefore the impact of this overestimation in daily dose would have been mitigated. Alternate day dosing medications are relatively uncommon – it is usually only used when a drug is

being tapered off (e.g. GC), and even so, the duration of a tapered dose regimen is relatively short; therefore any misclassification in alternate day dosing prescriptions would be unlikely to have a major impact on the results, especially if the study has a large sample size. In addition, alternate-day GC therapy in GCA patients has been found to be associated with high rates of flares compared with daily treatment (70% versus 20%), therefore it is not recommended for use in clinical practice [319].

Results from my study indicate that CPRD-derived data is reliable to be used for analyses. Although there were some misclassifications in some important variables (e.g. number of tablets per day and frequency), the impact of these misclassifications was likely minimal. The findings from my study relating to GC starting dose, average daily dose, cumulative dose and treatment duration were all comparable to other published literatures, suggesting that there is no major difference between the CPRD-derived data and my extracted data, which was, comparatively, a lot more labor intensive due to some involvement of manual screening of the free text in the “dosage instructions” variable.

7.3. Strengths and Limitations

7.3.1. Strengths

This is to date the largest population-based longitudinal study specifically examining the incidence of DM in PMR and/or GCA patients. The novel rolling cumulative dose and WCE methods used in this study has allowed the quantification of DM risk associated with dosage, duration and timing of oral GC exposure to be determined, which is crucial to facilitate decision making in clinical practice. To date, only conventional methods (e.g. cumulative dose, current dose) have been used to determine the risk of DM associated with GC use. There are limitations with the use of conventional methods as imperfect assumptions are often made with regards to the timing of GC use in relation to the outcome. For example, use of “current dose” models take into consideration only the existing dose taken, but ignore the impact of past doses, while “recent dose” models only take into consideration the most recent dose (e.g. past 30 days) but ignore all doses taken outside that defined time frame. Another typical example is the use of “cumulative dose” models, of which the model assumes that doses taken years ago have the same impact as doses taken recently. In contrast, the rolling cumulative dose model and WCE allow the assessment of risk based on the dose, duration and recency of GC dosing.

The use of CPRD as one of the largest routinely collected electronic health data that spanned primary care practices across UK and linked to the mortality registry is an important strength of this study. In addition, the data is also contemporary and up-to-date (generated after 1/1/1998); therefore results from this study provide a better idea of risks associated with current clinical practice. This would have been very different if data from the early or mid-nineties were used, as the diagnoses and treatment could have been very different then. Another important strength is the representativeness of this database. When compared with the 2011 UK census, CPRD patients were reported to be broadly representative of the UK population in terms of age, sex and ethnicity [9]. Not only is it a generally good representation of the general population in the UK, it also has a relatively large sample size with long-term follow-up data, which is crucial for study of relatively rare diseases such as PMR and GCA to allow a more efficient estimation of association between exposure and outcome. The electronic aspect of prescribed medications not only decreases the rate of possible data entry errors, but also allows a more efficient way of maintaining patient's confidentiality and privacy.

CPRD has been widely used in research for decades, and a number of methods have been used to assess validity, including internal and external validations [320]. A systematic review of validation and validity of diagnoses of different disease domains in CPRD (e.g. musculoskeletal system, respiratory system, circulatory system etc), reported a high estimate of validity, though the quality of reporting was inadequate to permit a clear interpretation [320].

The retrospective aspect of this study allows access to information readily available; therefore the study would only need a relatively short period of data construction and data cleaning, as compared to prospective studies that requires information to be collected as follow-up is carried out.

7.3.2. Limitations and Potential Biases

This section will discuss a few limitations and potential biases that were considered within the data sources and related to the design of this study. These potential biases were addressed carefully as they may influence the validity of the estimates of the true relationship between the study exposure and outcome measure.

7.3.2.1. Limitations of Study Design

7.3.2.1.1. New User/ Inception Cohort Study Design

One of the issues relating to the inception cohort or new user study design and the exclusion of patients without GC prescriptions (i.e. because PMR and GCA diagnoses would be unlikely) was that there were no “controls” without GCs. The presence of a control group would have allowed a more robust conclusion to be made - that any change observed in the active GC treatment group is more likely due to the treatment being studied, rather than to other factors. The use of the inception cohort design, however, was appropriate for my diseases of interest, as patients with PMR and/or GCA would almost be exclusively treated with GCs upon diagnosis. Therefore, the comparison between a high dose regimen and a low dose regimen would be a good depiction of real-world clinical practice. One alternative is to use the case-control study design, but there are challenges associated with the use of this study design. One of the biggest challenges is to identify controls from the general population as a comparator. These controls are likely to be different to patients diagnosed with PMR and/or GCA, and would also be less likely monitored for DM by the GPs. Another limitation is the lack of general population sample to allow comparison of those getting type 2 DM anyway. To date, there is only one study that looked at the incidence of type 2 DM in primary care between 1991 and 2000 using CPRD [321], of which a comparison may be inappropriate as the time frame of my study was between 1998 and 2016. Even if a comparison were possible, it would also be extremely difficult to clinically differentiate between the diagnosis of “steroid-induced DM” and “non-steroid induced DM”. It is therefore possible that some of the incident type 2 DM cases recorded in primary care were actually steroid-induced DM.

Another limitation is the reduced sample size because only those who were newly diagnosed with PMR and/or GCA and had at least one GC prescription during the study period can be included. However, the final sample size of my study population (n=23,048) was still large compared to other studies.

7.3.2.1.2. Observational Study Design

One of the key limitations relating to the use of an observational study design is the inability to deduce a cause-and-effect relationship between the exposure and outcome. While my data do show a fairly convincing association between higher GC doses and DM risk, I am unable to prove conclusively that the association is causal. The presence of unmeasured confounders cannot be ruled out, which I will be addressing in Section

7.3.2.4. The use of an observational study design however, is the most practical and feasible for determining the association between GC dose and DM risk for the following reasons. Firstly, both PMR and GCA, although not uncommon, are still relatively rare compared to other common diseases like coronary heart disease or asthma. It would therefore be unpractical to use a randomized controlled trial (RCT) study design, as patient recruitment would likely take a long time. Secondly, DM is not an acute disease; therefore time is needed for the event to occur, of which it would be very time-consuming and expensive to conduct using the RCT study design. Thirdly, using routinely collected primary care data such as CPRD has many advantages, which include a large sample size, long-term follow-up data and provides information on "real-world" use and practice.

7.3.2.2. Misclassification Bias

7.3.2.2.1. Misclassification Bias of Diagnosis

Misclassification bias is another common issue of concern in routinely collected health data. The criteria for classification of PMR/GCA by the British Society for Rheumatology (BSR) [7, 24] were not available in the dataset for diagnosis confirmation; therefore the diagnosis of PMR and GCA were solely defined based on recorded physician diagnosis in primary care.

Diagnosis of PMR and GCA is a challenge in clinical practice. For PMR, overlap in symptoms with other co-morbidities, presence of multiple co-morbidities and the lack of an established diagnostic test have been identified as contributors to diagnostic uncertainty [310]. For GCA, in addition to its relative rarity compared to other musculoskeletal diseases, primary care GPs are often faced with the frequently non-specific nature of early GCA symptoms, as well as its high prevalence of similar symptoms in the general population [32, 322], which often leads to a delay to diagnosis or misdiagnosis [322-324]. An additional complexity of primary care data is that the absence of a Read code for the disease is interpreted as an absence of the disease itself, resulting in a higher positive predictive value [320], but lower sensitivity. One of the possible reasons may be due to variations between GPs in coding diagnoses in the patient's electronic health record, or if the information was entered as free text, then it may be missed out on. There is also a possibility that patients with mild disease or with atypical presentations might be less likely to be diagnosed [260].

To date, there has only been one validation study for the diagnosis of PMR, which reported a wide variation in the diagnosis of PMR among general practitioners and hospital specialists [325]. It is worth noting though, that the study was done in the early 1990s and only represented a small subset (Norwich) of the UK population. The diagnosis of GCA in CPRD has been previously validated by comparing electronic CPRD records with typical symptoms and clinical response to GCs, and the authors reported a validity of 91% [8]. To minimize the likelihood of PMR and GCA misclassification in my study, only those with at least one GC prescription were included in the study. Since both PMR and GCA are inflammatory diseases with clinical symptoms, it is therefore unlikely that patients would be left untreated if they truly had the disease. Furthermore, the median age of my study population was in the mid-seventies, with nearly two thirds of them being female, which was consistent with other published studies [260, 258, 11, 298].

7.3.2.2.2. Misclassification Bias of Outcome

As with PMR and GCA, the diagnosis of DM was also primarily defined based on recorded physician diagnosis in primary care. The parameters for criteria classification by World Health Organization (WHO) [326] were largely missing, as specific markers (e.g. HbA1c, fasting plasma glucose) are not routinely collected in primary care settings.

Another major challenge pertaining to the outcome is its definition. The outcome of interest for this PhD was GC-induced DM. There is however, no appropriate measure to validate this, thus there is a possibility of misclassification of outcome. One of the precautionary steps I did was to only take into account cases of new-onset DM occurring within the initial two years of follow-up. Non-steroid induced type 2 DM is well documented as a progressive disease, primarily characterized by a progressive decline in beta-cell function and worsening of insulin resistance over time [327]. Various studies have reported that the development of non-steroid induced type 2 DM generally occurs between 29 months to 10 years in those with baseline impaired fasting glucose reading, depending on risk factors [328-332]. Furthermore, the highest incidence of type 2 DM is reported to be between 40 and 69 years of age in the National Diabetes Audit, UK [333]; and between 45 and 64 years of age by the Centers for Disease Control and Prevention (CDC) [334] in the US, suggesting that those who were at risk of developing DM is likely to have had developed DM in middle age or earlier; while the median age for my study population was 74 years old. It is therefore reasonable to assume that the development of new-onset DM in my study population was likely to be

a consequence of GC therapy (for at least over 50% of the patients), and not a phenomenon pathogenically linked with the traditional risk factors for DM. One could argue that there might be a subgroup of predisposed patients who progressed from latent to manifest DM exacerbated by high-dose or prolonged GC therapy, while this is plausible, it is unlikely to involve the whole study population considering the large sample size and magnitude of effect in DM risk. Another possible misclassification relating to the outcome was that patients may have had undiagnosed DM, but when prescribed with GCs, DM testing is likely to have been done as part of routine screening due to its known risk. As a result, DM was discovered, and although not due to GC treatment, it may have been considered as related to GC use in my study just because routine screening revealed the condition. While cases as such may be possible, it is unlikely to involve the whole study population and would be likely to apply equally to the low-dose and high-dose patient groups.

The quality of recording of DM in CPRD has been evaluated in a cross sectional study [335], of which the effect of miscoding and misclassification on incidence estimates was evaluated. Results from the study showed that the incidence of diabetes did not increase and was consistent with other reports [336, 251] if only the diagnoses codes were used. In my study, only the diagnoses codes were used. In addition, only practices that met the quality marker (up-to-standard) date were included.

7.3.2.2.3. Misclassification Bias of Exposure

The possibility of misclassifying the main exposure (i.e. oral GC dose) also cannot be ruled out. Prescription records in CPRD merely indicate that the drug has been prescribed and dispensed, but it does not provide any information on how much of the drug was actually taken by patients. It is possible that patients had their prescriptions filled, but never taken, or in some cases taken initially and then discontinued, or taken as needed or intermittently. My analyses showed that approximately half of the prescription database for oral GCs had a “as directed” or “unknown” instruction. Hence, I assumed that one tablet was taken per day to calculate the daily dose if no other information was available. The application of this conservative assumption may have resulted in an underestimation in DM risk associated with the dose prescribed. In any case, the resulting misclassification of exposure is likely to be non-differential, resulting in a bias toward the null – which is of less concern, given that the results indicated statistical significant associations with clinically important estimates.

Another limitation of my study relating to the main exposure is the inability to account for medications prescribed by specialists in secondary care. This includes the non-oral GCs (i.e. intravenous, intra-arterial or intramuscular GCs) that would have been likely used in my patient population, especially during initial treatment or during disease flares. In certain circumstances, use of non-oral GCs may have been recorded, but it would only represent a very small sample, which does not give a clear reflection on the actual total use of non-oral GC use at the GP level. However, in practice, oral GCs remain the mainstay of treatment, and any other mode of administration is likely to be for a short duration; and while it may affect the magnitude of the risk, it is unlikely to alter the overall conclusion.

Another possible limitation relating to GC exposure was the use of monthly dose regimens in the assessment of DM risk. The monthly dose regimens were used to make the analyses more tractable, but the use of weekly or daily dose regimens may reveal more details on the actual risk of developing DM.

7.3.2.3. Time-related Bias

Time-related bias, such as immortal-time bias, defined as a period of cohort follow-up or observation time during which the outcome of interest cannot occur [337], is another common issue in pharmacoepidemiology studies. To prevent the introduction of time-related bias, I used a time-dependent definition of exposure that properly classifies the appropriate duration of person-time of study follow-up as “exposed” or “unexposed”, according to the date of start and end of drug use. In other words, the start of follow-up was unrelated to the prescribed GC medication. The same set of inclusion and exclusion criteria were applied to the entire study population. Another challenge often associated with treatment effects is misclassification of duration of use as treatment use and dose often vary with time. This issue was addressed by using the extended time-varying Cox model, rolling cumulative model and the weighted cumulative dose analysis, of which oral GC dose was allowed to vary over time.

7.3.2.4. Unmeasured Confounding

Unmeasured confounding is defined as confounding associated with variables not included in the data under study, leading to confounding bias [338]. This is particularly prominent in routinely collected data, as some variables needed for the analysis may not be routinely collected in clinical practice. One particular type of unmeasured confounding is confounding by indication, which refers to a determinant of the outcome

parameter that is present in people at perceived high risk or poor prognosis and is an indication for the intervention [339]. This means that differences in treatment may partly originate from the differences in indication for medical intervention such as the presence of risk factors for particular health outcomes. It is however, not a major concern in this study, as the selection of GC use is unlikely to be related to DM risk. There is however, still a possibility that clinicians may have been less willing to prescribe higher GC doses, or use a more rapid tapering regimen to control disease activity in obese patients who are at higher risk of developing DM. The reverse could also be possible – clinicians may be more likely to give higher GC doses to overweight or obese patients on the basis that higher body weight corresponds with higher drug clearance, and therefore an increased dose is required. This is known as reverse causation, of which a predisposition to DM (or a DM diagnosis) may have resulted in a need for higher GC doses. This is however, very unlikely as GC clearance is correlated to lean body weight rather than adipose weight as adipose tissue has little metabolic activity [340]. Normal-weight patients have a total body weight consisting of lean and adipose body weight in an approximate 4:1 ratio, while the lean:adipose weight ratio in obese patients has been reported to be 3:2 [341]. This indicates that obese patients have a lower lean weight, of which an increased GC dose is not required, as a higher drug clearance is unlikely. Another possibility is the issue of disease severity, which is particularly difficult to measure precisely in routinely collected health data. Because GCs are the mainstay of treatment for PMR and GCA, it was not possible to disentangle the effect of the disease from the effect of the treatment. It is however known that systemic inflammation itself can also induce a state of insulin resistance [265, 97] so it is plausible that the inflammatory disease itself (PMR or GCA) could have contributed to the risk of DM. In addition, some medications commonly prescribed to elderly patients may also contribute to the risk of DM (e.g. thiazide diuretics, beta-blockers, niacins and statins).

7.4. Recommendations

It is indisputable that patients with PMR and/or GCA would need to be treated with GC despite the increased risk of developing DM in the initial stages of their treatment. The challenge is that they are not just treated with GC, but often initiated on high starting doses as well, with longer duration of treatment compared to patients with other systemic inflammatory conditions [342]. While the GC doses are tapered gradually over time, these patients are often still susceptible to the risk of developing GC-induced DM, as reported in this study. Therefore, good DM management in this patient population is essential as long standing DM is often associated with microvascular and macrovascular complications. There is however, little evidence and guidance on how patients with GC-induced DM should be managed, especially among the elderly, which represents my patient population.

A multidisciplinary EULAR task force on GC therapy has developed a few recommendations for the management of medium to high dose GC therapy in rheumatic diseases. “Medium to high dose” GC therapy was defined as > 7.5mg but ≤ 100mg PED daily [342], which fits well into the range of treatment doses that PMR and/or GCA patients usually receive in the initial stages of treatment. Although the recommendations were not specific for the management of GC-induced DM in PMR and/or GCA patients, some of the general approaches were still applicable and may be adopted by GPs in primary care settings. The recommendations are as follow [342]:

1. Explain to patients and their family and/or carers the aim of medium/high dose GC treatment and the potential risk associated with such therapy.
2. Discuss measures to mitigate any risks, including diet and regular exercise.
3. Provide an accessible resource to promote best practice in the management of patients using medium/high dose GCs to GPs, such as having a website on the benefits and risks of GC treatment, advising how to manage inter-current illnesses and acute situations.
4. Before starting medium/high dose GC treatment, any co-morbidities predisposing to adverse events such as DM should be given consideration. Patients with these co-morbidities require tight control (i.e. more intensive monitoring and adjusting medication, if needed) to manage the risk/benefit ratio. Glucose monitoring before start of therapy and during therapy is also advised.
5. Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of under-treatment.

6. Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of under-treatment and development of adverse events such as DM.
7. All patients should have appropriate monitoring for clinically significant adverse events, including DM.

The UK Joint British Diabetes Societies for Inpatient Care (JBDS-IP) has put together a set of guideline on the management of hyperglycemia and steroid (glucocorticoid) therapy [343], which again, although non-specific to PMR and/or GCA patients, still applicable to the management of GC-induced DM in these patient populations. Although the guideline includes management for in-patient care, it also includes management for GC-induced DM in general; therefore it is still applicable to my patient population. In addition, capillary blood glucose (CBG) testing is accessible to patients in the community and self-monitoring may be done at home.

The guideline recommends a Hemoglobin A1c (HbA1c) baseline level to be taken prior to the commencement of GC therapy. For patients without a pre-existing diagnosis of DM, the CBG testing should be done at least once daily, preferably prior to lunch or evening meals, or alternatively 1-2 hours post lunch or evening meal. If the initial CBG is less than 12mmol/L, then the once daily testing is adequate. If a subsequent CBG is found to be greater than 12mmol/L, then the frequency of testing should be increased to four times daily before meals and before bed. In cases where the CBG is consistently greater than 12mmol/L (i.e. on two occasions over 24 hours), then patients should be started on treatment.

The guideline also recommended a few treatment options for DM patients who are taking once daily GC. One of the treatment options is to use a sulphonylurea such as gliclazide. Gliclazide is a short acting sulphonylurea, usually taken once daily to promote insulin release from the pancreatic beta cell. It can be titrated to a maximum of 320mg daily, with a maximum of 240mg in the morning. Gliclazide is relatively cheap compared to other anti-diabetic medications, but the risk of hypoglycemia associated with this medication may be problematic for older patients, especially for PMR and/or GCA patients who are mostly above 70 years of age. Therefore, older patients prescribed with gliclazide should be counselled on the common signs and symptoms of hypoglycemia and actions to take if it does occur.

Another oral treatment option is the use of a biguanide such as metformin that works by decreasing glucose production and increasing insulin sensitivity. It can be titrated to a maximum of 1g twice a day. Benefits of metformin include its low cost, favourable weight profile and low risk of developing hypoglycemia, which makes it a safer option to use during GC tapering, especially for patients without a previous history of DM who may be less likely to have their blood glucose tested consistently. Although considered as one of the safest first-line therapy in DM, use of metformin in the elderly should still be monitored. One of the main concerns with the use of metformin is an increased risk of lactic acidosis, especially in the elderly; though the American Diabetes Association in its consensus report has clarified that despite early concerns, the evidence for an increased risk is minimal [344]. It should however, be used with caution in patients with reduced renal function. It should not be used in those with an estimated glomerular filtration rate (eGFR) of less than 30mL/min, and for those with an eGFR between 30-60mL/min, the dose should be reduced [345, 346].

One of the non-oral treatment options is the use of the basal human insulin (i.e. Humulin I, Insuman Basal or Insulatard). Morning administration of these basal insulins may be beneficial as they closely fit the glucose excursion induced by a single dose of oral GC in the morning. The recommended starting dose is 10 units of insulin with a daily dose increase between 10-20%, titrated to the blood glucose level, although dose increments of up to 40% have been shown to be required in some patients [347]. As with all insulins, one of the major concerns is the risk of hypoglycemia. Given the heterogeneity of the older PMR and/or GCA patient population, the risk of hypoglycemia must be carefully considered before using an insulin regimen to achieve an aggressive target for hyperglycemia control [344]. The management and treatment algorithm for patients without a pre-existing diagnosis of DM has been summarized in Figure 7.1, of which the information was adapted from the JBDS-IP – Management of hyperglycemia and steroid (glucocorticoid) therapy guideline [343].

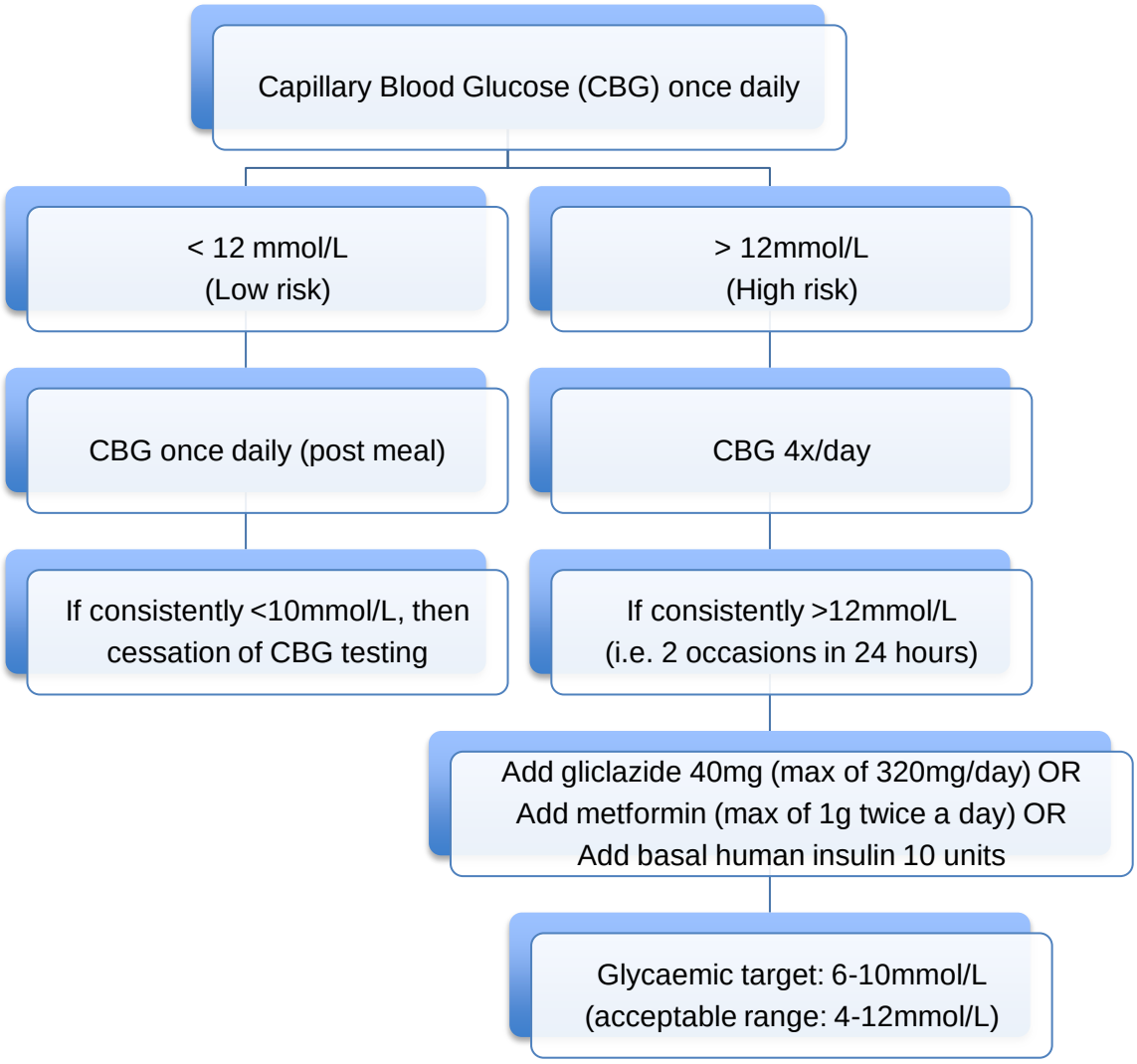


Figure 7.1: Management and treatment algorithm for GC-induced DM in patients without a pre-existing diagnosis of DM, adapted from JBDS-IP guideline [343].

Treatment of DM in PMR and/or GCA patients will always remain a challenge, especially with this group of patients being older in age and more susceptible to the adverse effects of anti-diabetic medications due to age-related changes in the pharmacokinetics and pharmacodynamics affecting drug disposition. This is often aggravated by polypharmacy and complex regimens associated with multiple comorbidities. Shared decision making has been advocated as the most appropriate approach to improving the quality of these important medical decisions [348, 349]. Key aspects of this shared decision include the establishment of an ongoing partnership between the patient and provider, information exchange, deliberation on choices and finally, making the decisions [350]. One key element of improving communication and involving patients in the decision making process is to find congruence between patient goals and clinicians goals [344]. Clinicians should first educate patients on the significance of risk factors and then discuss the possible harms and benefits of each intervention to reduce these risk factors. Equally important is to discuss treatment options and the possible adverse events that accompany each treatment options. The treatment doses should always be balanced against the need to use the lowest effective dose for the shortest period of time to avoid adverse events [6].

7.5. Future Work

One area of interest would be to identify and stratify patients who are at high risk and explore their DM risk associated with GC use. One potential group of patients who are considered to be at high risk is those with relapsed or refractory PMR/GCA. These are the patients with the highest unmet need and the hardest to manage. It is likely that current treatment is sub-optimal in these patients, thus leading to frequent relapse. They are also likely to have a pre-existing high cumulative GC burden with greater concomitant medication usage and greater burden of co-morbidities [351, 281, 352]. For GCA patients, tocilizumab has recently been made available as an alternative drug, but the cost of it is high, and use of this drug is likely to only be in a very small selected patient population based on eligibility [100]. Another group of patients who are at high risk of developing DM are PMR/GCA patients with co-morbidities, especially those with hypoalbuminemia or liver disease. Hypoalbuminemia is quite common at presentation of PMR/GCA as it is a feature of the acute phase response. GCs are metabolized primarily in the liver; therefore the presence of liver disease prolongs the half-life of GCs. This would result in patients having a reduced drug clearance, and possibly an increased risk of GC-related toxicity such as DM. GCs are known for their high protein binding property, with non-linear protein bound attributes. Since only the unbound form is the biologically active compound, only the measurement for the free

fraction of GC in the plasma is relevant. Patients with hypoalbuminemia will have a higher free fraction of circulating GC in the plasma; therefore they may be at higher risk of experiencing GC-related toxicities such as DM. It is possible that what is most detrimental in regard to DM is not just the higher dose, but the combination of higher dose with active uncontrolled inflammation.

The reversibility of GC-induced DM in PMR/GCA patients is also an area of potential interest. The effect of GC has been reported in some case reports as being transient and reversible, of which the effect of GC doses on endocrine metabolism is expected to return to baseline as GC doses are reduced over time [20, 353]. This issue is however, not well studied and remains a challenge in observational studies, as it is likely to be confounded by many factors, including but not limited to treatment dose, duration, lifestyle changes, co-morbidities, as well as use of other medications.

The impact of BMI on the risk of type 2 DM is a well-investigated topic, with many studies reporting that higher BMI was associated with a higher risk of developing type 2 DM [354-356], though it is unknown if higher BMI has any impact on the development of steroid-induced DM. BMI was not accounted for in my study for reasons mentioned in Section 5.6.4, but it is definitely important to consider the role of BMI and obesity in the development of steroid-induced DM, especially the timing and duration of obesity, as well as pre-diabetic status. Though prolonged duration of obesity (or higher BMI) has been reported to cause additional metabolic changes, leading to the development of hyperglycemia and diabetes [357, 358], there is still a huge research gap on whether this hypothesis applies to steroid-induced DM.

As discussed in section 7.2.2.1, the issue of how GCs should be tapered in the safest and most effective way with minimal relapses is of great importance. Since relapse rates have been reported to be associated with higher initial GC dose and faster GC tapering rates, one of the possible areas of interest is to compare the risk of DM in patients with a tapering dose regimen versus a fixed dose regimen. This can be done by comparing the tapering dose regimen from my study population with Kirwan's proposed fixed dose regimen - starting dose of 15mg daily for six weeks then 12.5mg daily for six weeks, then a 10mg maintenance dose for one year, with a 1mg/per month taper thereafter if needed [313]. Another approach would be to do a RCT of tapering dose regimen versus a fixed dose regimen. This approach would however, require a significant amount of time for patient recruitment, as well as a significant amount of financial resources to implement the trial. In addition, patients with PMR and/or GCA may develop flares throughout their course of disease, potentially more so for patients

on low dose regimens. Therefore an additional challenge would be to incorporate a protocol on how these patients should be managed if flares occur, which would add complexity to the design protocol.

As discussed in section 7.2.4, there is a substantial deviation in the prescribing pattern of oral GC in patients with GCA (with or without PMR) compared to EULAR guidelines. One of the possible next steps is to impute the initial GC doses using a data driven algorithm with clinical input and reevaluate the risk of DM associated with oral GC cumulative dose.

As discussed in the section 7.3.2.3.3, a weekly dose regimen could be explored instead of using the monthly dose regimen. The WCE method could also be applied to quantify the risk of other GC-related toxicities such as osteoporosis, cataract, adrenal suppression etc.

The last issue of interest is related to the current GP prescribing software that does not seem to deal well with gradual GC taper regimens as often used in PMR and/or GCA. Even if recorded, the complete regimen is not available as only the dose would be recorded (i.e. 5 4 3 2 1), but not the duration for each of the specific doses. This might be an area that needs to be improved by the GP software developers.

7.6. Conclusions

Although GCs have been used extensively for decades in the treatment of PMR and GCA, the risk of developing DM has not been quantified in relation to the dose, duration and timing of oral GC cumulative dose exposure. Applications of the rolling cumulative dose and WCE models have provided great clinical insight on the etiologically pertinent time window of past exposure and on the relative importance of GC doses taken at different time periods. My study finding demonstrates that patients with PMR and/or GCA have a substantially increased risk of developing DM within the first few months of treatment initiation. Implementation of a screening program for DM should be considered in these patient groups. This study has also provided insights on the prescribing pattern of oral GC in primary care as compared to guidelines. Understanding the pattern of use in a real-world clinical setting is crucial, as patients with PMR and/or GCA often require long-term treatment with GC. Optimum doses of GC are needed to control disease symptoms and prevent potential relapses, yet the doses should also be as low as possible and prescribed for the shortest duration possible to minimize the occurrence of GC-induced DM. Since treatment with GC is absolutely essential in these patient groups, effective prevention and efficient management of side effects such as DM associated with GC therapy is crucial to reduce morbidity and increase quality of life in these patients.

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APPENDICES

APPENDIX 1: 'MeSH' Search Terms

Population

1. polymyalgia rheu*
2. giant cell art*
3. temporal art*
4. large vessel vasculiti*

Intervention/ Exposure

5. glucocortico*
6. corticostero*
7. steroid*
8. predniso*

Outcomes

9. diabet*
10. impaired glucose tolerance
11. glucose
12. hyperglyc*
13. HbA1C
14. glycated h*
15. #13 or #14
16. HOMA
17. obes*
18. overweight
19. BMI
20. body mass index*
21. #19 or #20
22. waist*
23. hip-waist ratio
24. hip waist ratio
25. #22 or #23 or #24
26. #1 or #2 or #3 or #4
27. #5 or #6 or #7 or #8
28. #9 or #10 or #11 or #12 or #15 or #16 or #17 or #18 or #21 or #25

Final Search Terms

#26 and #27 and #28

APPENDIX 2: MOOSE Guidelines for meta-analyses and systematic reviews of observational studies

Sections	Criteria
Reporting of background	• Problem definition • Hypothesis statement • Description of study outcome(s) • Type of exposure or intervention used • Type of study designs used • Study population
Reporting of search strategy	• Qualifications of searchers (e.g. librarians and investigators) • Search strategy, including time period included in the synthesis and keywords • Efforts to include all available studies, including contact with authors • Databases and registries searched • Search software used, name and version, including special features used, use of hand searching (e.g. reference lists of obtained articles) • List of citations located and those excluded, including justification • Method of addressing articles published in languages other than English • Methods of handling abstracts and unpublished studies • Description of any contact with authors
Reporting of methods	• Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested • Rationale for the selection and coding of data (e.g. sound clinical principles or convenience) • Documentation of how data were classified and coded (e.g. multiple raters, blinding, and interrater reliability) • Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate) • Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results • Assessment of heterogeneity • Description of statistical methods (e.g. complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated • Provision of appropriate tables and graphics
Reporting of results	• Graphic summarizing individual study estimates and overall estimate • Table giving descriptive information for each study included • Results of sensitivity testing (e.g. subgroup analysis) • Indication of statistical uncertainty of findings
Reporting of discussion	• Quantitative assessment of bias (e.g. publication bias) • Justification for exclusion (e.g. exclusion of non-English-language citations) • Assessment of quality of included studies

APPENDIX 3: ISAC Protocol

Safety and associated costs of glucocorticoid therapy for the treatment of chronic inflammatory diseases

Date of ISAC Approval:
28/07/2016

Lay Summary:
Steroids are a group of medications that are widely used to treat many different diseases of long duration, such as asthma, and their prolonged use has increased over time in the UK despite their side effects. Side effects can develop within days (e.g. mental illness) or after prolonged use (e.g. high blood pressure). Side effects can have a major impact on quality of life, independence and wellbeing, particularly as people get older, and lead to many hidden costs to the individual and the healthcare system. For many conditions there are no approved alternatives to steroids and it is important we obtain accurate information about the side effects of treatment and the full costs of these to the individual and the NHS. This information is very helpful in building a strong case to support the introduction of new treatment, which have been shown to be effective in clinical trials, into the NHS. With CPRD data we intend to develop new methods that allow clinicians and policy makers to balance risks and benefits of steroid treatment in patients with common long-lasting diseases. This will be achieved first by describing the side effects and what makes these more likely to happen; and then developing methods that help to identify patients at higher risk of developing side effects.

Technical Summary:
The aim of this research is to develop tools that enable clinicians and policy decision makers to balance harms and benefits of glucocorticoids for the treatment of chronic inflammatory diseases. This will be achieved through; 1) description of glucocorticoid toxicity profiles and its predictors; and 2) development of treatment stratification tools for clinical evaluation to accurately identify patients at increased risk of developing toxicity. This research will enable informed personalised adaptation of treatment for patients identified with high risk of toxicity (e.g. earlier dose reduction or use of glucocorticoid-sparing therapies), improvement of clinical guidelines and quality of care and equity in health care provision, ultimately improving long-term patient outcomes. To estimate toxicity rates and describe toxicity patterns we will expand our phenotyping work to identify patients with common chronic inflammatory diseases and adverse events. The description of common patterns of toxicity, overall and in patients with different underlying diseases and age groups, and the exploration of the relative importance of duration of medication and dose will inform the construction of risk prediction models to enable patient risk stratification according to risk of toxicity development and the future development of decision cost-models to guide policy and clinical decision making.

Health Outcomes to be Measured:
Glucocorticoid toxicity All-cause hospitalisation Hospitalisation for toxicity Death for toxicity All-cause mortality

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APPENDIX 4: R Codes

Appendix 4.1. Cohort

DETERMINE START OF FOLLOW-UP DATE

```
# Determine the latest date of the following criteria
# Criteria 1: Diagnosis of PMR and/or GCA (Variable = first_diagnosis)

# Criteria 2: Start of CPRD: 1/1/1998
Cohort$CPRDStart_DailyD <-as.Date("1998-01-01")

# Criteria 3: UTS date + 1 year
Cohort$NewUTS <- ymd(Cohort$uts) %m+% years(1)

# Criteria 4: GP Registration date + 1 year
Cohort$NewRegDate <- ymd(Cohort$current_registration_date) %m+% years(1)

# Criteria 5: At least 18 years old (Set birth year to 07/01/YYYY format)
Cohort$month <- "7"
Cohort$day <- "1"
Cohort$DOB <- ISOdate(Cohort$birth_year, Cohort$month, Cohort$day)
Cohort$DOB <- strptime(Cohort$DOB, format = "%Y-%m-%d")

##### Calculate baseline age during study entry / age at diagnosis #####
Cohort$Age_days <- difftime(Cohort$study_entry_date, Cohort$DOB , units =
c("days"))
Cohort$Age_years <- Cohort$Age_days/365.25

# Check if any patients below 18yo (None!)
Below18 <- Cohort [which(Cohort$Age_years < 18),]

# Aggregate by ID and find latest date
Cohort2 <- Cohort %>% mutate(LatestDate = pmax(first_diagnosis,
CPRDStart_DailyD, NewUTS, NewRegDate, na.rm = TRUE))
```

Note (1): All the data was checked twice
Note (2): I compared the study entry date constructed from my cohort with the given study entry date, they were identical.

DETERMINE BASELINE DM STATUS

```
# File 1: Anti-DM Medication
# Aggregate by ID and find earliest Rx date
AntiDM_Earliest <- setDT(AntiDM)[order(eventdate), head(.SD, 1L), by="patid"]

# File 2: DM Diagnosis
# Create subset of patients with any kind of DM - H/O, T1, T2, secondary DM,
Unspecified, gestational, steroid induced
AnyDM <- subset(DM_Dx, DM_Dx$X0..H.O.All!="NULL" |
DM_Dx$X1.Diab.1.All!="NULL" | DM_Dx$X2.Diab.2.All!="NULL" |
DM_Dx$X3.2ry.diab.All!="NULL" | DM_Dx$X4.Diab.unspec.All!="NULL" |
DM_Dx$X5.Gestation.All!="NULL" | DM_Dx$X6.Steroid.related.All!="NULL")
```

```
# Determine earliest DM diagnosis date
AnyDM <- AnyDM %>% mutate(Earliest_DMDx = pmin(AnyDM$X0..H.O.All,
AnyDM$X1.Diab.1.All, AnyDM$X2.Diab.2.All, AnyDM$X3.2ry.diab.All,
AnyDM$X4.Diab.unspec.All, AnyDM$X5.Gestation.All, AnyDM$X6.Steroid.related.All))

# Merge files (Cohort, Anti-DM medication & DM diagnosis)
# Stage 1: Merge cohort with those who were on antiDM drugs
CPRD1 <- merge(Cohort, AntiDM_Earliest, by=c("patid"), all.x=TRUE)

# Stage 2: Merge cohort+those on meds with those who had a DM diagnosis
CPRD2 <- merge(CPRD1, AnyDM, by=c("patid"), all.x=TRUE)

# Select earliest of the following dates (DM diagnosis or Anti-DM prescription)
# Earliest_DMDx = earliest date of DM diagnosis
# eventdate = earliest prescription date for antiDM medications
CPRD2 <- CPRD2 %>% mutate(EarliestDM_Dx_Rx = pmin(CPRD2$Earliest_DMDx,
CPRD2$eventdate))

# Populate the "EarliestDM_Dx_Rx" rows with missing values using the
"Earliest_DMDx" values (as some patients have a DM diagnosis but did not have any
DM prescription)
CPRD2$Earliest_DMDx[CPRD2$Earliest_DMDx == "NULL"] = NA
CPRD2$Earliest_DM_Dx_Rx_Final <- CPRD2$EarliestDM_Dx_Rx
CPRD2$Earliest_DM_Dx_Rx_Final <- ifelse
(!is.na(CPRD2$Earliest_DM_Dx_Rx_Final), CPRD2$Earliest_DM_Dx_Rx_Final,
CPRD2$Earliest_DMDx)

# Determine DM status prior to GCA/PMR diagnosis
CPRD2$DM <- "NoDM"
CPRD2$DM[(CPRD2$Earliest_DM_Dx_Rx_Final >= CPRD2$first_diagnosis)] <- "DM"
CPRD2$DM[(CPRD2$Earliest_DM_Dx_Rx_Final < CPRD2$first_diagnosis)] <-
"Pre_existing_DM"

# Exclude patients with pre-existing DM
CPRD3 <- subset(CPRD2, DM!="Pre_existing_DM")

# Exclude patients with T1DM
# Definition of T1DM = Have a diagnosis date of Type1 DM + only on Insulin & not on
any other oral hyperglycemic agents
CPRD3$T1DM <- "Not_T1DM"
CPRD3$T1DM[(CPRD3$X1.Diab.1.All!="NULL") & (CPRD3$insulin=="1") &
(CPRD3$antidiab=="NULL")] <- "T1DM"
CPRD3_NoT1DM <- subset(CPRD3, T1DM!="T1DM")
```

DETERMINE DEATH DATE

```
# Combine death date from ONS & HES (priority given to ONS)
CPRD3_NoT1DM$death_date <- CPRD3_NoT1DM$ONS_death_date
CPRD3_NoT1DM$death_date <- ifelse (CPRD3_NoT1DM$ONS_death_date ==
"NULL", CPRD3_NoT1DM$CPRD_death_date, CPRD3_NoT1DM$ONS_death_date)

# Categorize into 4 groups
CPRD3_NoT1DM$Event_First [(CPRD3_NoT1DM$death_date!="NULL") &
(CPRD3_NoT1DM$DM=="DM")] <- "DM_Died"
CPRD3_NoT1DM$Event_First [(CPRD3_NoT1DM$death_date!="NULL") &
(CPRD3_NoT1DM$DM=="NoDM")] <- "NoDM_Died"
```

```
CPRD3_NoT1DM$Event_First [(CPRD3_NoT1DM$death_date=="NULL") &
(CPRD3_NoT1DM$DM=="DM")] <- "DM_Alive"
CPRD3_NoT1DM$Event_First [(CPRD3_NoT1DM$death_date=="NULL") &
(CPRD3_NoT1DM$DM=="NoDM")] <- "NoDM_Alive"
```

DETERMINE END OF FOLLOW UP DATE

```
# Determine the earliest date of the following variables:
# 1: Latest contact (latest date where the GP submitted the data)
# 2: Transfer out date / Deregistration date (patient left the GP)
# 3: Death
# 4: DM
CPRD3_NoT1DM <- CPRD3_NoT1DM %>% mutate(End_of_FU =
pmin(latest_contact, transfer_out_date, death_date, Earliest_DM_Dx_Rx_Final, na.rm
= TRUE))

# Calculate FU duration (from study entry date to end of FU)
CPRD3_NoT1DM$FU_Days <- difftime (CPRD3_NoT1DM$End_of_FU,
CPRD3_NoT1DM$study_entry_date, units=c("days"))

# Exclude patients with negative follow-up dates
CPRD_Final <- subset(CPRD3_NoT1DM, FU_Days >= 0)

# Replace those with "0" FU days as 0.1
CPRD_Final$FU_Days [CPRD_Final$FU_Days <1] <- 0.1
CPRD_Final$FU_Years <- CPRD_Final$FU_Days/365.25
```

RESTRICT TO NEWLY DIAGNOSED PMR/GCA PATIENTS

```
New_Cohort <- subset(CPRD_Final, first_diagnosis>=study_entry_date)
```

Note: All the data was checked at every stage, especially the “NULL” & “NA” values

Appendix 4.2. Covariates

DETERMINE USE OF NON-ORAL GC DURING STUDY FU

```
# Merge cohort & Rx data
Covariates <- merge (New_Cohort, Covariate, by="patid")

# Create Y/N variables for all non-oral GC
Covariates$Non_OralGC_Use <- "Yes"
Covariates$Non_OralGC_Use[(Covariates$articgc=="NULL" &
Covariates$imgc=="NULL" & Covariates$rectgc=="NULL" &
Covariates$topgc=="NULL" & Covariates$inhgc=="NULL" &
Covariates$nasgc=="NULL" & Covariates$unkgc=="NULL")] <- "No"
Covariates$Non_OralGC_Use[(Covariates$fludrocortisone=="1")] <- "No"

# Change from long to wide format
Unique_Reshape <- reshape(Unique, idvar = "patid", v.names = "Non_OralGC_Use",
timevar = "Non_OralGC_Use", direction = "wide")

Unique_Reshape$NonOralGC_Final <- "No"
Unique_Reshape$NonOralGC_Final[(Unique_Reshape$Non_OralGC_Use.Yes=="Yes
")] <- "Yes"
Unique_Reshape$NonOralGC_Final[(Unique_Reshape$Non_OralGC_Use.Yes=="Yes
" & Unique_Reshape$Non_OralGC_Use.No=="No")] <- "Yes"
```

FAMILY HISTORY OF DM

```
# Merge cohort & family history file
DM <- merge (New_Cohort, DM_Dx, by="patid")

# Create Y/N variables
DM$FamilyHx <- "Yes"
DM$FamilyHx[(DM$X.2..F.H.CPRD=="NULL" & DM$X.2..F.H.HES=="NULL" &
DM$X.2..F.H.ONS=="NULL" & DM$X.2..F.H.All=="NULL")] <- "No"
```

BMI

```
# Impute missing data for height (using mean)
BMI_Mean <- aggregate (height.m.~patid, BMI_Weight, mean, na.rm=TRUE)

# Calculate BMI
BMI_Merged$Calculated_BMI <- BMI_Merged$weight.kg. /
(BMI_Merged$Mean_height * BMI_Merged$Mean_height)

# Categorize BMI as either baseline, prebaseline or postbaseline (by comparing event
date vs. study entry date)
BMI$DateDiff <- difftime (BMI$eventdate, BMI$study_entry_date, units = "days")
BMI$DateDiff_Year <- BMI$DateDiff/365.25

# Baseline = BMI recorded ON or within 1 year prior to entry
# Pre-baseline = Average of all recorded values recorded during the period between 2-
5 years BEFORE study entry
# Post-baseline = Average of all recorded values recorded within 1 year AFTER study
entry

BMI$BMI_Cat <- "NR"
```

```
BMI$BMI_Cat[(BMI$DateDiff_Year > 0) & (BMI$DateDiff_Year <= 1)] <- "BMI_Post"
BMI$BMI_Cat[(BMI$DateDiff_Year > -1) & (BMI$DateDiff_Year <= 0)] <-
"BMI_Baseline"
BMI$BMI_Cat[(BMI$DateDiff_Year > -5) & (BMI$DateDiff_Year <= -1)] <- "BMI_Pre"

# Subset baseline data only
BMI_Baseline <- subset(BMI, BMI_Cat=="BMI_Baseline")

# Find mean of BMI for each patient at baseline (n=8276)
BMI_Final <- aggregate (BMI_Final~patid+BMI_Cat, BMI_Baseline, mean,
na.rm=TRUE)
```

SMOKING

```
# Baseline = Smoking status recorded ON or within 1 year prior to entry (If have
evidence of ex-smoker - change!)
# Pre-baseline = All smoking status codes recorded BEFORE the year prior to entry
and use the higher level of exposure
# Post-baseline = All smoking status codes recorded in the year AFTER the date of
entry and use the higher level of exposure
# For patients w/o data at baseline, use last observation carried forward or backwards

# Categorize smoking as either baseline, prebaseline or postbaseline (by comparing
event date vs. study entry date)
Smoking$DateDiff <- difftime (Smoking$eventdate, Smoking$study_entry_date, units =
"days")
Smoking$DateDiff_Year <- Smoking$DateDiff/365.25
Smoking$Smoking_Cat <- "Unknown"
Smoking$Smoking_Cat[(Smoking$DateDiff_Year > 0) & (Smoking$DateDiff_Year <=
1)] <- "SmokingStatus_Post"
Smoking$Smoking_Cat[(Smoking$DateDiff_Year > -1) & (Smoking$DateDiff_Year <=
0)] <- "SmokingStatus_Baseline"
Smoking$Smoking_Cat[(Smoking$DateDiff_Year > -2) & (Smoking$DateDiff_Year <= -
1)] <- "SmokingStatus_Pre"

# Determine highest level of exposure (2 examples shown)
Smoking$Smoking[(Smoking$SmokingStatus=="Non smoker (1)" &
Smoking$Smoking_Cat=="SmokingStatus_Baseline")] <- "NonSmoker_Baseline"
Smoking$Smoking[(Smoking$SmokingStatus=="Ex smoker (2)" &
Smoking$Smoking_Cat=="SmokingStatus_Baseline")] <- "ExSmoker_Baseline"
```

Note: Checks were performed throughout the process

Appendix 4.3. Prescription Database

DETERMINE DOSING FREQUENCY

```
# Merge cohort & Rx data
Cohort_Rx <- merge (Rx, New_Cohort, by="patid")

# Select Rxs between study entry date to end of FU
CPRD <- subset (Cohort_Rx, prescription_date >= study_entry_date &
prescription_date <= End_of_FU)

# Create subset for oral GCs (exclude all non oral GCs)
Rx <- subset (CPRD, !orgc=="NULL")

# Extract information on frequency of use from "dosage instructions" variable (free text)
# Check how many unique dosage instructions (n=3016) – all these were screened
manually
Check.directions <- unique(Rx $dose)

# Categorize dosing frequency (2 examples shown for each category)
Rx[grep ("NOW", Rx$dose), "Directions"] <- "Stat"
Rx[grep ("STAT", Rx$dose), " Directions "] <- "Stat"

Rx[grep ("^AD", Rx$dose), " Directions "] <- "As directed"
Rx[grep ("^AS RECOMMENDED", Directions $dose), "Rx"] <- "As directed"

Rx[grep ("/DAY", Rx$dose), " Directions "] <- "OD"
Rx[grep ("2 TAB DAILY", Rx$dose), " Directions "] <- "OD"

Rx[grep ("EVERY OTHER DAY", Rx$dose), " Directions "] <- "EOD"
Rx[grep ("EOD", Rx$dose), " Directions "] <- "EOD"

Rx[grep ("PRN", Rx$dose), " Directions "] <- "PRN"
Rx[grep ("AS REQD", Rx$dose), " Directions "] <- "PRN"

Rx[grep ("A WEEK", Rx$dose), " Directions "] <- "Weekly"
Rx[grep ("WEEKLY", Rx$dose), " Directions "] <- "Weekly"

Rx[grep ("1EVERY3DAYS", Rx$dose), " Directions "] <- "2x/wk"
Rx[grep ("TWICE/WEEK", Rx$dose), " Directions "] <- "2x/wk"
Rx[grep ("1 MANE 1 EVENING", Rx$dose), " Directions "] <- "BD"
Rx[grep ("1 MANE 2 NOCTE", Rx$dose), " Directions "] <- "BD"

Rx[grep ("TID", Rx$dose), " Directions "] <- "TDS"
Rx$Rx [(Rx$dose=="ONE EVERY EIGHT HOURS")] <- "TDS"

Rx[grep ("THREE TIMES A WEEK", Rx$dose), " Directions "] <- "3x/wk"
Rx[grep ("THREE TIMES PER WEEK", Rx$dose), " Directions "] <- "3x/wk"

Rx[grep ("FOUR TIMES", Rx$dose), " Directions "] <- "4x/d"
Rx[grep ("QID", Rx$dose), " Directions "] <- "4x/d"

Rx[grep ("FIVE TIMES", Rx$dose), " Directions "] <- "5x/d"
Rx[grep ("5X DAILY", Rx$dose), " Directions "] <- "5x/d"
Rx[grep ("REDUCING", Rx$dose), " Directions "] <- "Taper"
Rx[grep ("54321", Rx$dose), " Directions "] <- "Taper"
```

```
Rx$Rx [(Rx$dose=="100MG")] <- "Unknown"
Rx$Rx [(Rx$dose=="AFTER FOOD")] <- "Unknown"

# Change frequency to "numeric" version (e.g. OD = 1)
Rx[grep ("Stat", Rx$Rx), "Frequency"] <- "1"
Rx[grep ("PRN", Rx$Rx), "Frequency"] <- "1"
Rx[grep ("As directed", Rx$Rx), "Frequency"] <- "0"
Rx[grep ("Unknown", Rx$Rx), "Frequency"] <- "0"
Rx[grep ("OD", Rx$Rx), "Frequency"] <- "1"
Rx[grep ("EOD", Rx$Rx), "Frequency"] <- "0.5"
Rx[grep ("Weekly", Rx$Rx), "Frequency"] <- "0.143"
Rx[grep ("2x/wk", Rx$Rx), "Frequency"] <- "0.286"
Rx[grep ("3x/wk", Rx$Rx), "Frequency"] <- "0.429"
Rx[grep ("BD", Rx$Rx), "Frequency"] <- "2"
Rx[grep ("TDS", Rx$Rx), "Frequency"] <- "3"
Rx[grep ("4x/d", Rx$Rx), "Frequency"] <- "4"
Rx[grep ("5x/d", Rx$Rx), "Frequency"] <- "5"
Rx[grep ("6x/d", Rx$Rx), "Frequency"] <- "6"
Rx[grep ("Taper", Rx$Rx), "Frequency"] <- "1"
```

Note: Checks were done on 18/1/18 & 24/6/18 & 21/9/19

DETERMINE NUMBER OF TABS PER DOSE

File 1: OD / EOD

```
# Create subset for OD & EOD dosing
OD <- subset (Rx, Directions == "EOD" | Directions == "OD")

# Check number of unique instructions (n=2138)
OD_Unique <- unique(OD[c("dose", "daily_dose", "Tabs_dose")])

# Conversion of MG to number of tabs
OD$Tabs_dose [(OD$dose=="10 MG DAILY" | OD$dose=="10 MG EVERY DAY") &
(OD$strength=="2.5mg")] <- "4"

# Check all "ML" related dosing – make sure that they were all per ML
OD$Tabs_dose [(OD$dose=="THREE 5ML SPOONSFUL TO BE TAKEN IN THE
MORNING")] <- "3" #5ml = 1 tab (5mg)
```

Note: The same process was related for all other files - BD, TDS, As directed etc

```
# Combine all individual files
A1 <- rbind (OD, BD)
A2 <- rbind (A1, TDS)
A3 <- rbind (A2, MT)
A4 <- rbind (A3, SPU)
A5 <- rbind (A4, AD)
A6 <- rbind (A5, WK)
Rx_Final <- rbind (A6, Taper)
```

Note: The length of file was checked to make sure that the total tallied the original Rx file

DETERMINE PREDNISOLONE EQUIVALENT DOSE

```
# Total unique GC products = 68
Products <- unique (Rx$product_name)
```

```
# Categorize PED (2 examples shown)
Rx[grep ("Deltacortril 2.5mg gastro-resistant tablets", Rx$product_name),
"predn_equiv"] <- "2.5"
Rx$predn_equiv [(Rx$product_name=="Dexamethasone 2mg/5ml oral solution")] <-
"2.667" #per ML
```

Note: Checks were done on all 68 products on 18/1/18 & 24/6/18

DETERMINE NUMBER OF TABS PER DAY

```
# Method 1: Tabs per day = Quantity prescribed / duration in CPRD+imputed from
“directions for use” variable
Data$Tabs_day_CPRD <- Data$quantity_prescribed/Data$duration

# Method 2: Tabs per day = Number of tabs per dose * frequency (for Rxs with
quantifiable instructions)
Data$Tabs_day <- Data$Tabs_dose*Data$Frequency

# Method 3: Tabs per day = Quantity prescribed / Difference in 2 consecutive dates
# Order in ascending order by dates & patid, then determine duration based on 2
consecutive dates
Data <- orderBy(~patid+prescription_date, data=Data)
Data <- Data %>% group_by (patid) %>%
  mutate (Duration_Dates = c(NA, round(diff.difftime(prescription_date, units="days"))))
%>%
  select(everything())

Data$Tabs_day_Dates <- Data$quantity_prescribed/Data$Duration_Dates

# Merge ALL THREE tabs per day variables
# Priority 1: Tabs_day_CPRD
# Priority 2: Tabs_day
# Priority 3: Tabs_day_Dates

# Merge first 2 & then check if there are any infinite, undefined or missing values!
Data$Tabs_day_Final1 <- Data$Tabs_day_CPRD
Data$Tabs_day_Final1 <- ifelse ((Data$Tabs_day_CPRD == "Inf" |
Data$Tabs_day_CPRD == "NaN" | is.na(Data$Tabs_day_CPRD)), Data$Tabs_day,
Data$Tabs_day_CPRD)

Check <- Data[c("Tabs_day_Final1", "Tabs_day_CPRD", "Tabs_day")]
sum(is.na(Data$Tabs_day_Final1)) #0
sum(is.infinite(Data$Tabs_day_Final1)) #0
sum(is.nan(Data$Tabs_day_Final1)) #0

# Merge 1, 2 & 3
Data$Tabs_day_Final <- Data$Tabs_day_Final1
Data$Tabs_day_Final <- ifelse ((Data$Tabs_day_Final1 == "0"),
Data$Tabs_day_Dates, Data$Tabs_day_Final1)
Check <- Data[c("Tabs_day_CPRD", "Tabs_day", "Tabs_day_Dates",
"Tabs_day_Final")]
sum(is.na(Data$Tabs_day_Final)) #11306
sum(is.infinite(Data$Tabs_day_Final)) #69812
sum(is.nan(Data$Tabs_day_Final)) #17

# Change all the missing and infinity data to zero
```

```
Data$Tabs_day_Final[Data$Tabs_day_Final == "Inf" | Data$Tabs_day_Final == "NaN"
| is.na(Data$Tabs_day_Final)] <- '0'
sum(is.na(Data$Tabs_day_Final)) #0
sum(is.infinite(Data$Tabs_day_Final)) #0
sum(is.nan(Data$Tabs_day_Final)) #0
```

DETERMINE DURATION

```
# 3 ways of calculating duration
# "duration" - given in CPRD (+imputed from directions for use variable)
# "Duration" - calculated: quantity prescribed / number of tabs per day
# "Duration_dates" - calculated: difference between 2 consecutive prescription dates

# Merge ALL THREE duration variables
# Priority 1: duration (Given in CPRD + imputed)

# Priority 2: Duration
Data$Duration_Calc <- Data$quantity_prescribed/Data$Tabs_day
# Merge first 2
Data$Dur <- Data$duration
Data$Dur <- ifelse ((Data$duration == "0"), Data$Duration_Calc, Data$duration)

# Priority 3: Duration_dates (Merge 1, 2 & 3)
Data$Dur_Dur <- Data$Dur
Data$Dur_Dur <- ifelse ((Data$Dur == "0" | Data$Dur == "Inf" | Data$Dur == "NaN" |
is.na(Data$Dur)), Data$Duration_Dates, Data$Dur)

# MEDIAN DURATION
# Calculate total duration for each patient by disease
CumDuration <- aggregate(Data$Dur_Dur, by=list(Data$patid, Data$disease), sum,
na.rm=TRUE)
summary (Data$Dur_Dur)

# For all missing duration - impute with median of 28 days
Data$Duration_Final <- Data$Dur_Dur
Data$Duration_Final[Data$Duration_Final == "0" | is.na(Data$Duration_Final)] <- '28'

# Replace those with > 90 days duration with the max of 90 days
Data$Duration_Final [Data$Duration_Final > 90] <- 90
```

ADDRESSING MISSING DATA FOR NUMBER OF TABS PER DAY

```
Data$Tabs_day_New <- Data$quantity_prescribed/Data$Duration_Final

# Replace all zero with this new tabs/day
Data$Tabs_day_Last <- Data$Tabs_day_Final
Data$Tabs_day_Last <- ifelse ((Data$Tabs_day_Final == "0" |
is.na(Data$Tabs_day_Final)), Data$Tabs_day_New, Data$Tabs_day_Final)

# Assume number of tabs=1 if not stated
Data$Tabs_day_Assumption <- Data$Tabs_day_Last
Data$Tabs_day_Assumption[Data$Tabs_day_Assumption == "0" |
is.na(Data$Tabs_day_Assumption)] <- '1'
```

DETERMINE DAILY DOSE

```
# Calculate total daily dose by patient (mg) - based on max daily dose cut off points
# Formula: Tabs_day_Final * PED

Data$DailyDose <- Data$Tabs_day_Assumption*Data$predn_equiv

# Replace those with > 120mg/day with 120mg
Data$DailyDose [Data$DailyDose > 120] <- 120
```

GC STARTING DOSE, DAILY DOSE, CUM DOSE & DURATION

```
#### PMR ####
# Calculate cumulative dose by patient
PMR$CumDose <- PMR$DailyDose*PMR$Duration_Final
Sum_PMR <- PMR %>%
  group_by(patid) %>%
  summarise(sum=sum(CumDose))

# Calculate cumulative duration by patient
Dur_PMR <- PMR %>%
  group_by(patid) %>%
  summarise(sum=sum(Duration_Final))

# Calculate average daily dose by patient
DailyDose <- merge (Sum_PMR, Dur_PMR, by="patid")
DailyDose $DD <- DD$CumDose/DD$CumDuration

# Calculate first dose
Earliest <- setDT(PMR)[order(prescription_date), head(.SD, 1L), by="patid"]
```

Note (1): Repeat process for PMR patients with DM & no DM
Note (2): Repeat process for GCA & GCA/PMR patients, then for DM & no DM subgroups

Appendix 4.4. Preparing Loops to Calculate Daily Doses

LOOP – DAILY DOSE

```
#### PMR only ####
# Use aggregate to calculate the total dose taken during follow up
PMR2$total.px.dose <- with (PMR2, Duration*DailyDose)
num.pts <- length(unique(PMR2$patid))
temp <- rep(NA, num.pts)
pt.df <- as.data.frame(temp)
pt.df$pt.aggregated.dose <- aggregate(PMR2$total.px.dose, by = list(PMR2$patid),
sum)

# Look at total dose summed from monthly doses
# Manipulate dates (Using Dx dates)
PMR2$dx.date <- as.Date(PMR2$first_diagnosis)
PMR2$dx.day <- as.numeric(PMR2$dx.date) # Default start date is 01-01-1970

# Manipulate dates (Using Rx dates)
PMR2$px.date <- as.Date(PMR2$prescription_date)
PMR2$px.day <- as.numeric(PMR2$px.date) # Default start date is 01-01-1970
last.px.taken <- max(PMR2$px.day + PMR2$Duration) # Take the last Rx and plus the
duration of that Rx (75 days)
num.days <- last.px.taken + 720 # Add dummy "0" for all patients who had less than 2
years of FU/Rx

# Manipulate dates (Using DM_Dx dates)
PMR2$dm.date <- as.Date(PMR2$DM_Dx)
PMR2$dm.day <- as.numeric(PMR2$dm.date) # Default start date is 01-01-1970

# Create empty array (by repeating 0 for the number of patients x number of days)
num.pts <- length(unique(PMR2$patid))
some.zeroes <- rep(0, num.pts*num.days)
dose.matrix <- matrix(some.zeroes, nrow=num.pts, ncol=num.days, byrow=TRUE)
dim(dose.matrix) # 19204, 18247

# Create a vector with patid within
pts <- unique(PMR2$patid)

# Use loops to fill dose matrix
num.PMR <- length(PMR2$prescription_date)
for(i in 1:num.PMR) {
  for(j in 1:PMR2$Duration[i]) {
    dose.matrix[which(pts==PMR2$patid[i]), PMR2$px.day[i]+j-1] <-
dose.matrix[which(pts==PMR2$patid[i]),
PMR2$px.day[i]+j-1] + PMR2$DailyDose[i]
  }
}

# Change the matrix to data frame format
dose.df <- data.frame(dose.matrix)

# Create another file for diagnosis of PMR / PMR
diags <- unique(data.frame(cbind(PMR2$patid, PMR2$dx.day)))
```

```
# Adjust to start on diagnosis day
adjusted.mx <- matrix (rep(0, num.pts*720), nrow=num.pts, ncol=720, byrow=T)
dim(adjusted.mx)

# Populate matrix with diagnosis day
for(i in 1:num.pts) {
  for (j in diags$dx.day[i]:(diags$dx.day[i]+719)) {
    adjusted.mx[i,j-diags$dx.day[i]+1] <- dose.matrix[i, j]
  }
}
adj.df <- data.frame(adjusted.mx)

# Aggregate daily dose by 30 days
PMR_30days<- do.call(cbind, by(t(adj.df), (seq(ncol(adj.df)) - 1) %/% 30, FUN =
colSums))
dim (PMR_30days)
PMR_30days <- data.frame(PMR_30days)

# Rename months
names(PMR_30days) <- c("Month00", "Month01", "Month02", "Month03", "Month04",
                       "Month05", "Month06", "Month07", "Month08", "Month09",
                       "Month10", "Month11", "Month12", "Month13", "Month14",
                       "Month15", "Month16", "Month17", "Month18", "Month19",
                       "Month20", "Month21", "Month22", "Month23")

# Calculate total dose over 2 years
pt.df$two.years <- with(PMR_30days, Month00 + Month01 + Month02 + Month03
                        + Month04 + Month05 + Month06 + Month07 + Month08 + Month09
                        + Month10 + Month11 + Month12 + Month13 + Month14 + Month15
                        + Month16 + Month17 + Month18 + Month19 + Month20 + Month21
                        + Month22 + Month23)

# Incorporate patid
PMR_30days$patid <- diags$patid

# Create another file for diagnosis of DM
DM <- unique(data.frame(cbind(PMR2$patid, PMR2$dm.day, PMR2$DM)))

# Merge PMR/PMR diagnosis & DM files
DMDx_Dx <- merge(diags, DM, by=c("patid"))

# Merge all files
Combo <- merge(DMDx_Dx, PMR_30days, by=c("patid"), all.y = TRUE)
names (Combo)
```

Note: Repeat process for GCA & PMR/GCA cohort

Appendix 4.5. Format Data For Survival Analysis

PREPARE FORMAT FOR SURVIVAL ANALYSIS

```
#### PMR ####
# Change from wide to long format
PMR_Long <- reshape(PMR, direction="long", varying=1:24, idvar='patid',
timevar="month", v.names="totaldose")

# Add start & stop (beginning & end of interval) variables
PMR_Long$Stop <- PMR_Long$month
PMR_Long$Start <- PMR_Long$Stop - 1

# Add "Event" column
# Diff_30 = DM date – Dx date, then divided by 30
PMR_Long$Event <- "0"
PMR_Long$Event [PMR_Long$DM=="1" & (PMR_Long$Diff_30 >= PMR_Long$Start
& PMR_Long$Diff_30 <= PMR_Long$Stop)] <- "1"

# Sort by patid and month
PMR_Long <- orderBy ( ~ + patid + month, data = PMR_Long)

# For each patient - determine the "max month" / end of FU
PMR_Long <- PMR_Long %>%
  group_by(patid, DM) %>%
  filter(cumsum(lag(Event == "1", default = FALSE)) < 1)

# Check WCE input (Data are in the right format for WCE estimation)
checkWCE(WCE_PMR_Final, id = "patid", event = "Event", start = "Start", stop =
"Stop", expos = "totaldose")
```

Note: Repeat process for GCA & PMR/GCA cohort

Appendix 4.6. Kaplan-Meier Survival Analysis

KAPLAN-MEIER ANALYSIS

```
# Stratify by disease
KM[grep ("DM", KM$DM), "Diabetes"] <- 1
KM[grep ("NoDM", KM$DM), "Diabetes"] <- 0

fit <- survfit(Surv(KM$FU_Years, KM$Diabetes) ~ KM$Disease, data = KM)
ggsurvplot(fit, data = KM) # Basic plot

ggsurvplot(fit, data = KM,
risk.table = TRUE,
pval = TRUE,
conf.int = FALSE,
xlim = c(0,2),
xlab = "Follow-up Duration (years),
ylim = c(0.8,1),
pval.coord = c(0.8, 0.9),
break.time.by = 0.5,
ggtheme = theme_light(),
legend.title = "Disease", legend.labs = c("PMR", "GCA and PMR/GCA"),
risk.table.y.text.col = T,
risk.table.y.text = FALSE)
```

Note: Repeat for gender & age (by tertiles, quartiles & quintiles)

Appendix 4.7. Extended Time-Varying Cox for Cumulative Dose

TIME VARYING COX – CUMULATIVE DOSE

```
## PMR ##
Mod1 <- transformBy("patid", Cum.dose = cumsum(totaldose), data = PMR)
cum.fit <- coxph(Surv(Start, Stop, DM1) ~ FamilyDM + NonOralGC +
I(Cum.dose/10000) + I((Cum.dose)*(Cum.dose)/100000000), data = Mod1)
cum.fit
cox.zph(cum.fit)
summary (cum.fit)

# Note: Repeat for each individual covariate; as well as the GCA & PMR/GCA cohort
```

Appendix 4.8. Rolling Cumulative Dose

ROLLING CUMULATIVE DOSE ANALYSIS

```
## PMR ##
# Month 1
patients <- unique(PMR$patid)
rolling1 <- vector()
for(i in patients) {
  doses4i <- subset(PMR, patid==i)
  n <- length(doses4i$month)
  temp <- cumsum(doses4i$totaldose)
  if (n>1) {
    temp[1:n] <- rollapply(doses4i$totaldose,1,sum)
  } # end of i loop
  rolling1 <- c(rolling1,temp)
} # end of j loop

PMR$rolling1 <- rolling1
```

Note: Repeat for months 2-24

```
# Time-varying Cox for rolling cumulative data
# Rolling - Month 1
cum.fit <- coxph(Surv(Start, Stop, DM.status) ~ FamilyDM + NonOralGC +
I(rolling1/1000) + I(rolling1*rolling1/1000000), data = PMR_Rolling)
cum.fit
cox.zph(cum.fit)
summary (cum.fit)
```

Note: Repeat for months 2-24

```
# Concordance for month 2 is the highest
# Calculation of HR in Excel using coefficient for month 2
with (PMR_Rolling, tapply (totaldose,month,summary))

Low Dose (month 1) = (LDose*coeff) + (LDose*Coeff(quadratic)* Coeff(quadratic))
High Dose (month 1) = (HDose*coeff) + (HDose*Coeff(quadratic)* Coeff(quadratic))
HR = exp (difference between high dose & low dose)
```

Note (1): Repeat for all doses from month 2-24
Note (2): Repeat process for GCA & PMR/GCA cohort

Appendix 4.9. Weighted Cumulative Dose

WCE ANALYSIS

```
#### PMR ####
# cutoff=1
wce.fit <- WCE(data = PMR, analysis = "Cox", nknots = 0, cutoff = 1, constrained = "R",
aic = FALSE, MatchedSet = NULL,
            id = "patid", event = "Event", start = "Start", stop = "Stop", expos = "totaldose",
            covariates = c("NonOralGC", "FamilyDM"))
wce.fit
plot(1:1,wce.fit$WCEmat, type="o", col="blue", xlab="Lag(months)", ylab="Weights")
print(wce.fit$WCEmat, digits=3)
```

Note: Repeat for cutoffs 2-24

```
# Lowest BIC at month 10
# Compare doses over the most recent 10 months between patients on high dose vs.
low dose
with (PMR, tapply (totaldose, month, summary))
LQ10 <- c(0.00, 0.00, 0.00, 0.00, 3.12, 19.21, 36.69, 60.0, 98.15, 263.3)
UQ10 <- c(210.0, 225.00, 250.0, 274.1, 300.00, 324.97, 367.50, 422.3, 500.00, 714.3)
HR.WCE(wce.fit, UQ10, LQ10, allres = TRUE)
```

Note: Repeat process for GCA & PMR/GCA cohort