Incidence, prevalence and treatment burden of Polymyalgia Rheumatica in the UK over two decades: a population-based study

Richard Partington MBChB, [1] Sara Muller PhD, [1] Toby Helliwell PhD, [1] Christian Mallen PhD, [1] Alyshah Abdul Sultan PhD [1]

[1]Arthritis UK Primary Care Centre, Keele University, Keele, UK

Corresponding author: Richard Partington

Clinical Research Fellow & General Practitioner

Keele University Research Institute for Primary Care & Health Sciences

Keele University, Staffordshire, ST5 5BG

Phone number: +44(0) 1782 7348889

Email: r.partington@keele.ac.uk

Word count (manuscript): 2,979

Word count (abstract): 247

ABSTRACT

Objectives:

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease in older people. Contemporary estimates of incidence and prevalence are lacking and no previous study has assessed treatment patterns at a population level. This study aims to address this.

Methods:

We extracted anonymised electronic medical records of patients over the age of 40 years from the Clinical Practice Research Datalink in the period 1990-2016. Absolute rate of PMR per 100,000 person-years was calculated and stratified by age, gender, calendar year. Incidence rate ratios were calculated using a Poisson regression model. Among persons with PMR, continuous and total duration of treatment with glucocorticoids (GC) were assessed.

Results:

5,364,005 patients were included who contributed 44 million person-years of follow-up. 42,125 people had an incident diagnosis of PMR during the period. The overall incidence rate of PMR was 95.9 per 100,000 [95% confidence interval 94.9, 96.8]. The incidence of PMR was highest in women, older age groups and those living in the South of England. Incidence appears stable over time. The prevalence of PMR in 2015 was 0.85%. Median (IQR) continuous GC treatment duration was 15.8 (7.9, 31.2) months. However, around 25% of patients received more than four years total GC therapy

Conclusions:

The incidence rates of PMR have stabilised. This is the first population-based study to confirm that a significant number of patients with PMR receive prolonged treatment with

GC; which can carry significant risks. The early identification of these patients should be a priority in future research.

INTRODUCTION

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease affecting older people. Its impact on patients' lives can be devastating; causing stiffness, severe pain and significant impairment to daily activities. [1] Glucocorticoids (GCs) remain the mainstay of treatment. [2]

The incidence and prevalence of PMR vary depending on geography; as latitude increases, so do PMR rates. [3] Previous studies have estimated the prevalence of PMR to lie between 0.1-1% [4,5] and incidence between 12 - 113 per 100,000 person years. [6–8] The majority of cases of PMR are treated in primary care (71-84%), [7,9] however much of the existing literature is based on secondary care hospital records. Therefore the burden of disease may have been underestimated. One large study (Smeeth et al) [10] used primary care data to estimate the incidence of PMR, reporting an overall rate of 84 per 100,000 person years, which was increasing with time. However, the final year of data published in this study was 2001 therefore more contemporaneous estimates of national data are needed to guide health service provision.

PMR is managed with gradually reducing glucocorticoid (GC) therapy, from moderate to low doses. [3] Joint guidance released by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) advises GC treatment for most patients with PMR should end by two years. [2] However, it has been suggested a large proportion of patients experience symptom flare upon cessation, or even reduction, of GC therapy (a "symptom tail'). [11]

The aims of this study are to quantify the overall incidence and prevalence of PMR in the UK using a large population-based database and investigate prescribing of GCs in those diagnosed with PMR.

METHODS

Data source and study population

Almost all healthcare in the United Kingdom (UK) is delivered by the National Health Service (NHS), a public system funded by taxation that provides free, or low-cost, healthcare to all residents. Around 90% of patient contacts in the UK with the NHS is via primary care [12] and 98% of people who live in the UK are registered with a General Practice. We utilised data from the Clinical Practice Research Datalink (CPRD; version July 2017), which contains data for around 17 million contributing patients within 718 (7.5% of the total) UK general practices. This database, containing electronic, coded information collected during the course of routine healthcare, is representative of the UK population in terms of age, sex and ethnicity [13] and has been used extensively for primary care research.

Incidence

We analysed data collected between 1st January 1990 and 1st January 2016. Patients contributed data after the latest of four events: 1) the study start date, 2) the date at which they became forty years old, 3) the date they registered at a participating practice plus six months, or 4) the date at which the practice was adjudged to reach internal quality standards; known as the 'up-to-standard' date.

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

Patients with a Read coded diagnosis of PMR (codes: N20..00 Polymyalgia rheumatica, N200.00 Giant cell arteritis with polymyalgia rheumatica) in their general practice record were included as incident cases. The first six months following registration with a practice

were excluded from the incidence analysis to avoid inclusion of prevalent cases which may have been incorrectly recorded at the point of registration. [10] To improve case ascertainment, we only considered PMR diagnosis to be valid if patients received at least two prescriptions for oral glucocorticoids; one within six months of the diagnosis date and the second within six months of the first prescription. [10] Patients could have a diagnosis of both PMR and giant cell arteritis (GCA). We looked only at the first occurrence of PMR; therefore all subsequent person-time and diagnostic codes were excluded. This process is summarised in supplement 1.

Treatment of PMR

To ascertain trends in the management of PMR, we assessed patterns of glucocorticoid (GC) prescribing in the incident cases of PMR. All GC prescriptions recorded in CPRD using medications from the British National Formulary (BNF) chapter 6.3.2 "Glucocorticoid therapy" were included. [14] CPRD contains information about quantity of medication prescribed, the number of units of medication to be taken each day and prescription duration. The algorithm used to define duration and dose of GC therapy (detailed in supplement 2) has been defined elsewhere [15] . Kaplan Meier survival methods were used to calculate the median duration of time from diagnosis until completion of continuous GC therapy. The end of a treatment course was determined to have occurred when no further GC prescriptions occurred for 90 days after the calculated duration of the previous prescription. Patients were censored if they were lost to follow up prior to stopping treatment. The 90-day period was chosen as it is the same as in previous CPRD based studies of medication use. [16] As part of a sensitivity analysis, we recalculated this duration 1) by increasing the interval between prescriptions to 6 months; or 2) in patients who received a diagnosis with another rheumatological condition

either prior to PMR diagnosis or in the two years subsequently; or 3) were referred to secondary care rheumatology services.

Statistical analysis

Crude incidence rates of PMR were calculated by dividing the total number of new cases by the total person-years of follow-up per 100,000 person-years. Incidence rates were stratified by age, gender, region and calendar year. Patient age was grouped into decades. Lexis expansion, [17] was used to calculate incidence rates by year following the study start date of 1st January 1990.

To compare the absolute rate of PMR by patient characteristics we used a Poisson regression model and calculated incidence rate ratios (IRR) for each covariate, including sex, age, region and calendar year of diagnosis. Age-adjusted incidences for each covariate were calculated with direct standardisation, using the sample population structure over the whole study.

For treatment pattern analysis, we calculated the average daily and total dose of GC prescribed, as well as cumulative treatment time and the total number of prescriptions and separate treatment courses each patient received. Dosage calculations were made by converting the strength of all medications to milligrams of prednisolone equivalent using the BNF conversion tables of equivalent anti-inflammatory doses. [14] Results were stratified by starting GC dose, age and sex.

Point prevalence of PMR was calculated for each calendar year by dividing the total number of patients who have received a diagnosis of PMR at any time in the past and were alive and contributing data on 31st December of that year (numerator) by the total number of patients alive and contributing data on that date (denominator) thereby including incident and

prevalent cases. As part of sensitivity analysis we recalculated prevalence in patients aged over 55 years in order to compare to a recent study.[9]

Ethical approval

This study was approved by CPRD's in-house Independent Scientific Advisory Committee (ISAC) (protocol number: 17_203RA). Statistical analyses were conducted using Stata version 15.1. [18]

RESULTS

Overall incidence

A total of 5,364,005 individuals contributed 43.97 million person-years of follow-up in the period 1990-2016. The total number of new occurrences of PMR that fulfilled the GC prescription criteria was 42,145. This equated to 90.4% of the total number of PMR cases recorded during this time. The overall incidence rate of PMR amongst patients aged 40 years and over was 95.9 [confidence interval (CI): 94.9, 96.8] per 100,000 person-years (table 1). Incidence rates were significantly higher at older ages: those aged>70 years were around ten times (IRR= 9.61 [95% CI 9.25, 9.98]) more likely to have PMR compared to those between the ages of 50 and 59 years. Females were 67% more likely to develop PMR compared to males (IRR= 1.67 [1.64-1.71]). A marked variation in incidence rates by region was found (figure 1), with rates highest in the South West region of the UK (124.1 [120.6-127.6]) and lowest in the North East (65 [59.5- 70.9]).

Table 1: Incidence rates of PMR, with incidence rate ratios, stratified by age, sex and region

	Number of events	Person time at risk (100,000 years)	Rate per 100,000 (95% Confidence Intervals)	Incidence Rate Ratio (95% Confidence Intervals) *	Age standardised Incidence Rate + + (per 100,000 person years)
Overall	42,145	439.70	95.9 (94.9, 96.8)		
Age					
40-49	409	129.96	3.2 (2.9, 3.47)	0.11 (0.10, 0.13)	
50-59	3139	113.75	27.6 (26.7, 28.6)	Reference	
60-69	9683	91.62	105.7 (103.6, 107.8)	3.80 (3.65, 3.96)	
70-79	17620	64.76	272.1 (268.1, 276.1)	9.61 (9.25, 9.98)	
80+	10405	33.05	314.9 (308.9, 321)	10.58 (10.17, 11.13)	
Sex					
Male	13,651	212.06	64.4 (63.3, 65.5)	Reference	69.22
Female	28,494	227.64	125.2 (123.7, 126.6)	1.67 (1.64, 1.71)	114.87
Region					
North East	500	7.69	65 (59.5, 70.9)	0.82 (0.75, 0.90)	62.54
North West	3843	49.36	77.9 (75.4, 80.4)	Reference	77.54
Yorkshire & the Humber	1286	16.91	76.1 (72.0, 80.3)	0.97 (0.92, 1.04)	73.62
East Midlands	1461	16.71	87.4 (83.1, 92.0)	1.14 (1.07, 1.21)	86.13
West Midlands	4207	41.45	101.5 (98.5, 104.6)	1.26 (1.21, 1.32)	98.44
East of England	4698	38.44	122.2 (118.8, 125.8)	1.56 (1.49, 1.62)	120.41
South West	4850	39.10	124.1 (120.6, 127.6)	1.45 (1.39, 1.51)	112.96
South Central	4754	46.70	101.8 (98.9, 104.7)	1.29 (1.24, 1.35)	101.57
London	2901	40.63	71.4 (68.9, 74.1)	0.97 (0.93, 1.02)	75.76
South East Coast	5167	43.89	117.7 (114.6, 121)	1.42 (1.36, 1.48)	110.23
Northern Ireland	991	13.76	72 (67.7, 76.6)	0.93 (0.87, 1.00)	73.06
Scotland	3154	40.05	78.7 (76.0, 81.5)	1.03 (0.99, 1. 08)	81.51
Wales	4333	45.01	96.3 (93.5, 99.2)	1.16 (1.11, 1.21)	90.05

* Adjusted for age, sex, region and year of diagnosis if not stratified as a covariate

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

Incidence of PMR over time

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

Table 2: Incidence rates of PMR by calendar year

Year	Number of events	Person years at risk per 100,000	Rate per 100,000 (95% Confidence Interval)	Incidence Rate Ratio (95% Confidence Interval)*	Age standardised Incidence Rate**	Point prevalence
Overall	42,145	439.70	95.9 (94.9, 96.8)			0.84%
1990	261	3.30	79.2 (70.1, 89.4)	Reference	76.3	0.34%
1991	336	4.54	74 (66.5, 82.3)	0.91 (0.77, 1.07)	69.4	0.38%
1992	401	5.27	76.1 (69, 83.9)	0.94 (0.80, 1.09)	72.1	0.44%
1993	464	6.02	77.1 (70.4, 84.4)	0.95 (0.81, 1.10)	71.9	0.49%
1994	476	6.55	72.7 (66.5, 79.6)	0.90 (0.77, 1.04)	68.4	0.52%
1995	548	7.06	77.7 (71.4, 84.4)	0.96 (0.83, 1.11)	74	0.57%
1996	657	8.06	81.5 (75.5, 88)	1.01 (0.87, 1.16)	77.4	0.60%
1997	754	9.34	80.7 (75.2, 86.7)	1.01 (0.88, 1.17)	77.6	0.62%
1998	863	10.69	80.7 (75.5, 86.3)	1.01 (0.88, 1.16)	76.5	0.64%
1999	1239	13.00	95.3 (90.1, 100.8)	1.20 (1.05, 1.38)	91.7	0.66%
2000	1537	15.85	96.9 (92.2, 101.9)	1.23 (1.08, 1.40)	93.7	0.68%
2001	1792	17.75	100.9 (96.4, 105.7)	1.28 (1.13, 1.46)	98.1	0.71%
2002	2131	20.05	106.3 (101.9, 110.9)	1.36 (1.20, 1.55)	103.5	0.74%
2003	2211	21.49	102.9 (98.7, 107.3)	1.33 (1.17, 1.51)	101.4	0.77%
2004	2296	22.96	100 (96, 104.2)	1.30 (1.15, 1.48)	98.5	0.79%
2005	2348	23.73	99 (95, 103)	1.30 (1.14, 1.48)	98	0.80%
2006	2389	24.12	99.1 (95.2, 103.1)	1.30 (1.15, 1.48)	97.7	0.83%
2007	2451	24.45	100.3 (96.4, 104.3)	1.32 (1.16, 1.50)	99.7	0.83%
2008	2495	24.60	101.4 (97.5, 105.5)	1.33 (1.17, 1.51)	100.7	0.85%
2009	2447	24.64	99.3 (95.5, 103.3)	1.30 (1.15, 1.48)	98.2	0.85%
2010	2497	24.34	102.6 (98.6, 106.7)	1.35 (1.19, 1.53)	101.6	0.86%
2011	2379	23.83	99.8 (95.9, 103.9)	1.32 (1.16, 1.50)	99.1	0.87%
2012	2268	23.50	96.5 (92.6, 100.6)	1.28 (1.12, 1.45)	95.9	0.87%
2013	2198	22.51	97.6 (93.6, 101.8)	1.29 (1.14, 1.47)	96.8	0.88%
2014	2037	20.58	99 (94.8, 103.4)	1.30 (1.14, 1.48)	97.2	0.88%
2015	1603	17.60	91.1 (86.7, 95.6)	1.20 (1.05, 1.36)	89.1	0.85%

* adjusted for region, age, gender

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

Glucocorticoid prescribing in PMR

In total 1,242,841 GC prescriptions were issued to patients after a diagnosis with PMR; of these 99.9% contained information about quantity of medication prescribed, and 48.3% about numeric daily dose. The median time taken for patients to stop continuous therapy was 1.31 years [Interquartile range [IQR] 0.65, 2.6] (figure 3). When the treatment gap was increased to six months, this increased to 1.88 years [0.93, 4.00]. When total GC treatment time was reviewed, median duration increased further to 1.93 years [0.95, 4.03], meaning around 25% of patients received more than four years of therapy. Among patients with a rheumatology diagnosis, or those referred to rheumatology, the median continual duration of GC therapy was greater at 1.49 [0.73, 3.16] and 1.55 years [IQR 0.79, 3.06] respectively. The median first and average daily doses of GC received (in milligrams of prednisolone equivalent) were

15mg [IQR 8, 21] and 6mg [IQR 4, 9] respectively. However, 7,138 (16.9%) patients received on average greater than 10mg GC per day. The median total dose of GC received (in grams of prednisolone equivalent) was 4g [IQR 2, 8]. Repeating analyses stratified by initial GC dose, age and sex was unremarkable, with only patients aged under 50 receiving significantly fewer prescriptions.

Prevalence of PMR

The point prevalence of PMR in 2015 amongst patients aged over 40 years was 0.85% (table 2) and was markedly different between males and females (0.6% and 1.16%). Prevalence increased to 1.7% (95% CI 1.69%, 1.71%) in patients aged over 55 years.

DISCUSSION

Main findings

This study estimates the burden of PMR in the UK to be slightly higher than previously estimated. In 2015 around one in 120 adults aged over 40 have received a diagnosis of PMR. Overall, the incidence of PMR during the study period 1990 to 2016 was 95.9 per 100,000 person years [94.9, 96.8]. However, after increasing until 2002, the incidence rate of PMR has stabilised. Almost 50% of PMR patients received more than two years of GC therapy following diagnosis, despite guidelines suggesting treatment should have ended.

Strengths and limitations

We have conducted the largest study yet to calculate a true estimate of the current incidence, prevalence and real-world treatment patterns of patients with PMR. This study uses robust methodology in a large, established database of patients who are representative of the UK population. It therefore is likely to be an accurate estimate of the true burden of PMR. Most patients with PMR are managed exclusively in primary care, [7,9] therefore this is the most appropriate setting to conduct this study.

A potential limitation is the ascertainment of cases. This was based on medical codes recorded by the primary care physicians, rather than research classification criteria[19] as there isn't sufficient detail in medical records and therefore CPRD to allow this. Patients may therefore subsequently be diagnosed with an alternative condition. However, using GC prescriptions to confirm PMR diagnosis is well established.[10,20].Greater than 90% of patients with a diagnosis of PMR received at least two GC prescriptions; showing the diagnosis is likely to be accurate in the vast majority of patients Furthermore, in the UK diagnoses made in secondary care are communicated to, and recorded in, primary care. Therefore although

this study examined patients in primary care, it will also contain information from secondary care.

Comparison to other studies

The highest incidence, 113 per 100,000 patients, previously reported was a study from the South West of England. [4] Although the overall incidence rate we found is lower than this, our estimate for this region was slightly higher (124.1 [120.6, 127.6]). In the United States, the most recent estimates of PMR rate reported by Raheel et al [8] was 63.9 per 100,000. This is lower than our figure. However, this study was not conducted in primary care and stricter diagnostic criteria, rather than codes were used. [21] We included patients from a much larger sample and whilst our PMR definition is not ideal, our estimates are broadly in line with other studies that have used clinical classification criteria. Therefore we believe that the risk of misclassification is minimal.

Women were more likely to develop PMR, with a female to male ratio of approximately 2:1, reflecting previous studies. [10] The strong association between older age and risk of developing PMR has been demonstrated before, with other studies reporting median age at diagnosis of 70 [9] or 75 years. [7] As rates of frailty, aches, pains, [22] and ESR measurements [30] increase with age, it is possible that primary care physicians may over diagnose PMR in at least some of these patients.

The prevalence of PMR has been found to vary between 0.1% and 1% in North Europe and North America. [4,23] The prevalence of 0.85% in 2015 calculated in our study is consistent with this. In a recent study in a single large GP practice in the south of the UK, Yates et al [9] reported a prevalence of 2.27% in those aged 55 years and over. In our data, the prevalence in

this group was 1.7%. This discrepancy could be explained by the higher incidence of PMR in the south and East of the UK.

Given PMR is known to preferentially affect people of Northern European descent, these results are likely to be generalisable to countries with significant number of people from this ethnic group. However, the incidence and prevalence figures reported in this study are less generalisable to countries at lower latitudes, as incidence and prevalence rates have been found to reduce with decreasing latitude. [5,24,25]

The incidence of PMR appears higher in the South of the UK compared to the North. This was also demonstrated by Smeeth et al. [10] Genetic associations between specific Human Leukocyte Antigen molecules and GCA have been found, [26] although none yet for PMR. [27] However, as no major variation has been found in the genetic make-up of people between different regions around the UK it is unlikely to be the reason for this difference. [28] Other potential reasons include an association between social class and PMR, a viral aetiological agent, or environmental differences such as reduced vitamin D levels in the North of the UK due to less sunlight exposure may lead to vitamin D deficiency being diagnosed preferentially.

Smeeth et al [10] found that the incidence of PMR in the UK was increasing until 2001, which we replicated. However following this date, the incidence rate plateaued.

With regards to GC therapy, 75% received a first dose between 8-21mg, which corresponds well to the recommended starting dose of 12.5-25mg. [2] The median duration of treatment of patients with GC in our sample is, however, less than that found by Shbeeb et al in their recent study into GC prescribing in a cohort of 359 patients with PMR in Olmsted County, Minnesota [29]. The median dose prescribed was similar, at around 5mg; but length of treatment was greater, with only 19% of patients discontinuing therapy in the first year of

316 treatment, compared to 27% in our data. A number of reasons for this difference could be
317 suggested, for example their patients may represent more severe variants of the condition;
318 they defined end of treatment as permanent discontinuation of GC therapy rather than a gap
319 of 90 days or 6 months and their inclusion criteria were stricter. Therefore some of the
320 patients included in our study may have gone on to be reclassified with a different condition
321 and have GC therapy curtailed earlier. Our sensitivity analyses of patients who had a record
322 of referral to secondary care rheumatology services, confirmed this group had longer
323 continuous and total treatment. Both studies agreed though that a significant proportion of
324 patients were subject to prolonged treatment with GCs.

325 Previous studies have shown that long-term GC treatment increases a person's risk of a wide
326 range of medical conditions. [30] This is the first study of a large population which confirms the
327 existence of a prolonged 'symptom tail' in PMR; wherein a significant number of patients
328 receive a higher average daily dose, a larger total dose, more individual prescriptions of GC
329 and receive their treatment over a longer period of time.

330 The reason behind this symptom tail could be a more severe subtype of PMR, or a different
331 underlying diagnosis, for example rheumatoid arthritis, for which referral for secondary care
332 review may be appropriate. Alternatively, it may represent GCs masking the symptoms of
333 other comorbidities which flare upon reduction of GC treatment or adrenal insufficiency
334 following prolonged GC use.
335

336 **Conclusion and clinical implications**

337 In conclusion, we have established the burden that PMR places upon the UK health service.
338 Due to the ageing population, the prevalence of PMR in the UK is increasing although
339 incidence rates appear to have stabilised. Analysis of high quality routinely collected primary

care data has enabled us to confirm that a significant proportion of patients with PMR receive prolonged treatment with GC, contrary to previously held norms that cure will be achieved within two years. Long term GC therapy is associated with a number of serious adverse effects, [30] which is both dose [31] and duration [32] dependent. Early identification of patients who are likely to be subject to prolonged GC therapy is a priority area for future research. These patients could then be prioritised for referral to secondary care for consideration of GC-sparing agents.

ACKNOWLEDGEMENTS

1. Funding disclosure

RP is funded by NHS Research and Infrastructure funds. CDM is funded by the NIHR Collaborations for Leadership in Applied Health Research and Care West Midlands, the NIHR School for Primary Care Research and a NIHR Research Professorship in General Practice, which also supports AAS (NIHR-RP-2014-04-026). TH is funded by an NIHR Clinical Lectureship in General Practice. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The funder was not involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

2. Competing interests

None

3. Author's contribution

Study design (RP, SM, TH, CM, AS), literature search (RP), data management (AS), data analysis, data interpretation (RP, AS), first draft and figures (RP), critical revision of drafts (SM, TH, CM, AS)

This study is based in part on data from the Clinical Practice Research Datalink GOLD database obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the author(s) alone

FIGURE LEGENDS

Figure 1

Incidence rates of PMR by region 1990-2016

Figure 2

Overall, male and female incidence of PMR 1990-2016 with 95% confidence intervals

Figure 3

Kaplan-Meier plot showing time to final glucocorticoid prescription, defined as a gap of greater than 90 days following end of previous prescription

REFERENCES

1. Helliwell T, Brouwer E, Pease CT, et al. Development of a provisional core domain set for polymyalgia rheumatica: Report from the OMERACT 12 Polymyalgia Rheumatica Working Group. *J Rheumatol*. 2016;43(1):182-186. doi:10.3899/jrheum.141179.

2. Dejaco C, Singh YP, Perel P, et al. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis*. 2015;74:1799-1807. doi:10.1136/annrheumdis-2015-207492.

3. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. *J Am Med Assoc*. 2016;315(22):2442-2458. doi:10.1001/jama.2016.5444.

4. Hayward RA, Rathod T, Muller S, Hider SL, Roddy E, Mallen CD. Association of Polymyalgia Rheumatica With Socioeconomic Status in Primary Care: A Cross-Sectional Observational Study. *Arthritis Care Res*. 2014;66(6):956-960. doi:10.1002/acr.22276.

5. Salvarani C, Gabriel SE, Michael O'Fallon W, Hunder GG. Epidemiology of polymyalgia rheumatica in Olmsted County, Minnesota, 1970–1991. *Arthritis Rheum*. 1995;38(3):369–373. doi:10.1002/art.1780380311.

6. Salvarani C, Macchioni P, Rossi F, et al. Epidemiologic and immunogenetic aspects of polymyalgia rheumatica and giant cell arteritis in northern Italy. *Arthritis Rheum*. 1991;34(3):351–356. doi:10.1002/art.1780340313.

7. Barraclough K, Liddell WG, du Toit J, et al. Polymyalgia rheumatica in primary care: a cohort study of the diagnostic criteria and outcome. *Fam Pract*. 2008;25(5):328-333.

8. Raheel S, Shbeeb I, Crowson CS, Matteson EL. Epidemiology of Polymyalgia Rheumatica 2000–2014 and Examination of Incidence and Survival Trends Over 45 Years: A Population-Based Study. *Arthritis Care Res*. 2017;69(8):1282-1285. doi:10.1002/acr.23132.

9. Yates M, Graham K, Watts R, MacGregor A. The prevalence of giant cell arteritis and polymyalgia rheumatica in a UK primary care population. *BMC Musculoskelet Disord*. 2016;17(1) (pagination):Arte Number: 285. ate of Pubaton: 15 Ju 2016.

10. Smeeth L, Cook C, Hall a J. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. *Ann Rheum Dis*. 2006;65(8):1093-1098. doi:10.1136/ard.2005.046912.

11. Mackie SL, Arat S, Da Silva J, et al. Polymyalgia rheumatica (PMR) special interest group at OMERACT 11: Outcomes of importance for patients with PMR. *J Rheumatol*. 2014:819-823. doi:10.3899/jrheum.131254.

12. Hippisley-Cox J, Vinogradova Y. Trends in consultation rates in general practice 1995/1996 to 2008/2009: analysis of the QResearch database. *London QResearch Inf Cent …*. 2009:1-24. http://www.hscic.gov.uk/catalogue/PUB01077/tren-cons-rate-gene-prac-95-09-95-08-rep.pdf.

13. Herrett E, Gallagher AM, Bhaskaran K, et al. Is the GPRD GOLD population comparable to the UK population? *Int J Epidemiol*. 2015;44(3):827-836. doi:10.1093/ije/dyv098.

14. Joint Formulary Committee. British National Formulary (online). https://www.medicinescomplete.com/mc/bnflegacy/64/. Published 2017. Accessed February 1, 2018.

15. Paskins Z, Whittle R, Sultan AA, et al. Risk of fracture among patients with polymyalgia rheumatica and giant cell arteritis: a population-based study. doi:10.1186/s12916-017-0987-1.

16. Vinogradova Y, Coupland C, Brindle P, Hippisley-Cox J. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. *BMJ*. 2016. doi:10.1136/bmj.i3305.

17. Hertz S. Wilhelm Lexis. In: Heyde CC, Seneta E, Crépel P, Fienberg SE, Gani J, eds. *Statisticians of the Centuries*. New York, NY: Springer New York; 2001:204-207. doi:10.1007/978-1-4613-0179-0_43.

18. StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorpLLC.

19. Dasgupta B, Cimmino MA, Kremers HM, et al. 2012 Provisional classification criteria for polymyalgia rheumatica: A European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Arthritis Rheum*. 2012;64(4):943-954. doi:10.1002/art.34356.

20. Pujades-Rodriguez M, Duyx B, Thomas SL, Stogiannis D, Smeeth L, Hemingway H. Associations between polymyalgia rheumatica and giant cell arteritis and 12 cardiovascular diseases. *Heart*. 2016;102(5):383-389.

21. Raheel S, Crowson CS M EL. Epidemiology of polymyalgia rheumatica 2000-2014: A population based study. *Arthritis Rheumatol*. 2016;68:4265-4266. doi:http://dx.doi.org/10.1002/art.39977.

22. Buckinx F, Rolland Y, Reginster J-Y, Ricour C, Petermans J, Bruyère O. Burden of frailty in the elderly population: perspectives for a public health challenge. *Arch Public Heal*. 2015;73(1):19. doi:10.1186/s13690-015-0068-x.

23. Eaton WW, Pedersen MG, Atladottir HO, Gregory PE, Rose NR, Mortensen PB. The prevalence of 30 ICD-10 autoimmune diseases in Denmark. *Immunol Res*. 2010;47(1-3):228-231.

24. Gonzalez-Gay MA, Garcia-Porrua C, Vazquez-Caruncho M, Dababneh A, Hajeer A, Ollier WER. The spectrum of polymyalgia rheumatica in Northwestern Spain: Incidence and analysis of variables associated with relapse in a 10 year study. *J Rheumatol*. 1999;26(6):1326-1332.

25. Gonzalez-Gay MA, Vazquez-Rodriguez T, Lopez-Diaz M, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. *Arthritis Care Res*. 2009;61(10):1454-1461. doi:10.1002/art.24459.

26. Carmona FD, Mackie SL, Martín JE, et al. A large-scale genetic analysis reveals a strong contribution of the HLA class II region to giant cell arteritis susceptibility. *Am J Hum Genet*. 2015;96(4):565-580. doi:10.1016/j.ajhg.2015.02.009.

27. González-Gay MA, Matteson EL, Castañeda S. Polymyalgia rheumatica. *Lancet*. 2017;390(10103):1700-1712. doi:10.1016/S0140-6736(17)31825-1.

28. Leslie S, Winney B, Hellenthal G, et al. The fine-scale genetic structure of the British population. *Nature*. 2015;519(7543):309-314. doi:10.1038/nature14230.

29. Shbeeb I, Challah D, Raheel S, Crowson CS, Matteson EL. Comparable Rates of Glucocorticoid Associated Adverse Events in Patients with Polymyalgia Rheumatica and Comorbidities in the General Population. *Arthritis Care Res (Hoboken)*. 2017;0(0):1-5. doi:10.1002/acr.23320.

30. Moghadam-Kia S, Werth VP. Prevention and treatment of systemic glucocorticoid side effects. *Int J Dermatol*. 2010;49(3):239-248. doi:10.1111/j.1365-4632.2009.04322.x.

31. Huscher D, Thiele K, Gromnica-Ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis*. 2009;68:1119-1124. doi:10.1136/ard.2008.092163.

32. Walsh LJ, Wong CA, Oborne J, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax*. 2001;56:279-284.