Full Title:

Comorbidities in patients with polymyalgia rheumatica prior to and following diagnosis: A case control and cohort study

Article type:

Research

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ABSTRACT

Objectives:

To determine the burden of comorbidities, including glucocorticoid (GC) related adverse effects, in patients with polymyalgia rheumatica (PMR) before and after diagnosis.

Methods:

We extracted anonymised electronic medical records of patients over the age of 40 years from the Clinical Practice Research Datalink from 1990-2016. Patients with PMR were individually matched on age, sex and registered General Practice to between three and five controls. The prevalence, cumulative probability and likelihood of a range of comorbidities was estimated. Odds ratios (ORs) and hazard ratios (HRs) were calculated using conditional logistic regression and Cox proportional hazards regression respectively, adjusted for a wide range of covariates.

Results:

31,984 patients with PMR were matched to 149,436 controls. PMR was prospectively associated with vascular disease (adjusted HR 1.23 [95% confidence interval (CI) 1.19, 1.28]), as well as respiratory (HR 1.25 [1.18, 1.32]), renal (HR 1.34 [1.30, 1.39]), and autoimmune diseases (HR 4.68 [4.35, 5.03]). Conversely, before PMR diagnosis, the risk of cancer (adjusted OR [OR] 0.89 [0.86, 0.93]) and neurological disease (OR 0.36 [0.33, 0.40]) was significantly lower. Patients with PMR had an increased risk of comorbidities associated with glucocorticoid (GC) use.

Conclusions:

Patients with PMR have a high comorbidity burden, both before and after diagnosis. Whilst further work is needed to more fully understand these associations, clinicians should be aware of the high prevalence of comorbid conditions in this group and the impact that treatment with glucocorticoids may have on comorbidity.

KEY WORDS

Polymyalgia rheumatica

Epidemiology

Comorbidity

Cohort

Case control

INTRODUCTION

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic condition that can have a devastating impact on patients' lives (1) and predominantly affects older people. (2) Classical symptoms of PMR include stiffness, pain and significant impairment to daily activities. (3) The most recent study of PMR epidemiology, in patients over 40 years old, estimated the incidence and prevalence of PMR to be 95.9 [94.9, 96.8] per 100,000 person years and 0.85% respectively. (4)

Glucocorticoid (GC) therapy is the most common treatment for PMR. Patients initially receive a moderate dose (between 12.5mg and 25mg prednisolone equivalent), which is gradually tapered. (5) The majority of cases in the UK (71-84%) are treated in primary care. (6,7) 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.(8) However, a recent report suggests that approximately 25% of patients receive more than four years of treatment, potentially exposing many more PMR patients to prolonged GC therapy and an increased risk of associated adverse effects. (4)

PMR affects older people, and can present with non-specific symptoms and atypical features, (especially early in the disease course), causing diagnostic and management challenges. (9) PMR symptoms can mimic a wide spectrum of other conditions, (10) such as cancer, (11) osteoarthritis and frozen shoulder. (9) The presence of comorbidities, (e.g. diabetes, osteoporosis) can influence the suitability of treatment options and is likely to affect prognosis. However, it is not known whether the morbidity profile of people with PMR is different to their peers without PMR before or after PMR diagnosis.

MATERIALS AND METHODS

Data source

The National Health Service (NHS) provides healthcare to all UK residents, and 98% of people in the UK are registered with a General Practice. Around 90% of patient contacts in the UK occur in primary care. (12) We utilised data from the Clinical Practice Research Datalink (CPRD; version July 2017), which contains data from 17 million contributing patients across 718 (7.5% of the total) 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 research. This study was approved by CPRD's Independent Scientific Advisory Committee (ISAC), (protocol number: 17_203RA).

Definition of incident PMR

The exposed group were patients aged 40 years and over with a diagnosis of PMR recorded in their electronic healthcare records (EHR). Each patient had a Read code diagnosis of PMR (N20..00 Polymyalgia rheumatica; N200.00 Giant cell arteritis with polymyalgia rheumatica) and two prescriptions of GCs, the first made within six months of PMR diagnosis, and the second within six months of the first. This replicates previous PMR studies performed in CPRD (14–16) and provides supporting information as to the accuracy of the diagnosis. In addition to these requirements, each had at least three years of continuous follow up prior to date of diagnosis with PMR (the index date).

Selection of controls

Each case was matched with up to five, and no fewer than three, controls. The matching criteria employed were: 1) year of birth +/- 3 years, 2) sex and 3) registered practice. The index date for each case was assigned to their matched controls, who were also required to have been contributing data on that date and for 3 years prior.

Study period

Two matched studies were undertaken, a retrospective case control study and a retrospective cohort study. For the case control study, patients became eligible for inclusion after the latest of four events: 1) the study start date (1st January 1990), 2) the date at which they became 40 years old, 3) the date they registered at a participating practice plus six months, or 4) the date at which the practice reached CPRD internal quality standards; known as the 'up-to-standard date'. Data in the first six months after a patient became eligible was excluded to reduce the risk of inclusion of prevalent diagnoses. Data collection ended one year prior to index date to minimise protopathic bias, as per previous case control studies of comorbidities. (17–20)
For the cohort study, all patients, and their corresponding matched set, with a previous record of diagnosis with the comorbidity of interest were excluded from the dataset. Each comorbidity was assessed in a separate analysis. Data collection began at the index date for each participant. Data collection ended at the earliest of five events: 1) the end of the study period (1st 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 of diagnosis with the comorbidity of interest.

Comorbidities of interest

Comorbidities were selected using a three-step process. First, all 17 comorbidities in the Charlson Comorbidity Index were included. The total index score was calculated to gauge the overall level of comorbidity. Second, this list was augmented with conditions that had been previously investigated in people with PMR, identified in a recently published systematic review. (21) The third stage involved discussion with experts in the diagnosis and management of PMR, including Rheumatologists and General Practitioners. Three of the study authors (SM, CDM and TH) work with groups representing people with PMR (e.g. the charity, $PMRGCA_{UK}$). Involvement in these groups allowed discussion with people affected by PMR and their views were taken into account when designing this study. After these discussions, adverse effects/complications attributed to long-term glucocorticoid (GC) treatment and other extra-articular autoimmune conditions were added.

Comorbidities were grouped into composite outcomes, increasing the study power to detect whether PMR has an effect on the overall risk of development of each type of comorbidity, particularly rarer outcomes. The final list of comorbid outcomes are described in supplementary table S1.

Each comorbidity was identified using medical codes. For some comorbidities, such as vascular disease and fractures, code lists from previous peer-reviewed studies were used. Where such a list was not available, lists were constructed using the CPRD Medical Browser v1.4.0. The code lists (available on request) were reviewed by two authors (RP and AAS).

Statistical analysis

Case control analysis

The Charlson Comorbidity Index score and the prevalence of the individual and composite comorbidities were calculated five, two and one year prior to index date. We categorised Charlson Comorbidity Index score as 0, 1, 2, 3 and ≥4, as per previous CPRD studies. (22)

Higher Charlson Comorbidity Index scores correlate with greater multi-morbidity and risk of mortality. (23) Conditional logistic regression was used to calculate the association of PMR with previous diagnosis of comorbid disease, accounting for matching. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The ratios were then adjusted for relevant covariates (see below).

Cohort analysis

Following index date, the Charlson score and cumulative prevalence of each comorbidity were calculated at index date, as well as one, two, five and ten years after. When calculating these, all diagnoses made prior to index date were included. The cumulative probability of disease is defined as an estimate of the total number of patients with the comorbidity (numerator) divided by the total number of patients contributing data to the study during that time period (denominator). This method takes into account loss to follow up.

Cox regression models with robust standard errors were used to calculate hazard ratios (HRs) with 95% CIs for the likelihood of incident comorbidity in exposed (with PMR) compared to non-exposed (without PMR) groups. In these models, all patients with a pre-existing diagnosis of the outcome were excluded from the analysis. In addition to covariates described below, these models were also adjusted for the variables age and sex. Each condition was assessed separately, and data collection ended at the first event of interest after index date. To preserve anonymity, and in line with CPRD policy, if the number of patients within a category was <5, this result was suppressed.

Covariates

Smoking status, alcohol consumption and body mass index (BMI) category were considered to be potential confounders and adjusted for in the models described above. Alcohol

consumption is recorded within CPRD as units of alcohol consumed per week. Because body mass index, levels of alcohol consumption, and smoking, vary during a person's life, then data recorded in CPRD will also. Therefore, for this study the most recent occasion this information was recorded prior to index date was used. This follows the methodology of other CPRD studies. (15)

Alcohol consumption data was divided into four categories: 1) never or current non-drinkers, 2) < 10 units of alcohol per week, 3) ≥10 or more units, or 4) missing. Smoking status was categorised as 1) never or currently ex-smokers, 2) smokers, or 3) missing. BMI was divided into five categories: 1) "underweight" (BMI <18.5), 2) "normal" (BMI 18.5-24.9), 3) "overweight" (BMI 25-29.9), 4) "obese" (BMI>=30) or 5) "missing". The categories created in this study follow convention in the interpretation of BMI. (24) The reference categories used for these covariates in the conditional logistic model were non-smokers, no alcohol consumption and "normal" BMI. (15,17)

Data were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, (25) and analysed using Stata software, version 15.1. (26)

RESULTS

Study demographics

We identified 31,984 patients with incident PMR who were matched to 149,436 controls. The characteristics of the cases and controls are described in table 1.

Charlson Comorbidity Index

Overall comorbidity burden (Charlson Comorbidity Index) was greater in patients with a diagnosis of PMR compared to matched controls both before and after index date. Compared to controls, the Charlson score and the proportion of patients with PMR with at least one comorbidity was higher at each time point (table 2).

Retrospective analysis of comorbidities

The prevalence and risk of a pre-existing diagnosis with vascular (adjusted OR 1.04 [95% CI 1.01, 1.07]), respiratory (OR 1.24 [1.21, 1.28]), autoimmune (OR 1.32 [1.25, 1.39]), psychiatric (OR 1.15 [1.12, 1.19]) and infectious diseases (OR 1.39 [1.35, 1.43]), were significantly higher in cases compared to controls (figure 1, supplement S2 and S3). Conversely, the prevalence and risk of cancer (OR 0.89 [0.86, 0.93]) and neurological diseases (OR 0.36 [0.32, 0.40]) were significantly lower among patients with PMR.

The prevalence and likelihood of individual comorbidities were broadly similar to their composite groups. Exceptions to this included a significant reduction in the risk of cerebrovascular disease (OR 0.89 [0.85, 0.93]), and no significant difference in risk of diagnosis of melanoma, prostate cancer or colorectal cancer.

Prospective analysis of comorbidities

The cumulative probability (including pre-existing diagnoses) of all composite and individual outcomes are presented in table 3. The likelihood of new diagnoses (excluding pre-existing diagnoses), are displayed in figure 2 and supplement S3. The risk of any vascular (adjusted HR 1.23 [95% CI 1.19, 1.28]), respiratory (HR 1.24 [1.21, 1.28]), autoimmune (HR 4.68 [4.35, 5.03]), psychiatric (HR 1.29 [1.21, 1.36]) and ophthalmological (HR 1.37 [1.32, 1.42]) diseases, as well as glucocorticoid related infections (HR 1.26 [1.22, 1.31) was statistically higher in people with PMR compared to controls. Conversely, the risk of neurological diseases was lower (HR 0.89 [0.84, 0.93]). However, no significant difference in the overall risk of a new diagnosis of cancer after index date was seen [HR 0.98 (0.94, 1.01)]. The cumulative probability and likelihood of individual comorbidities were similar to their composite outcomes.

DISCUSSION

Main findings

Compared to matched controls, patients with PMR were found to have higher rates of comorbid diseases both before and after diagnosis date. There was a significantly increased risk of vascular, respiratory, renal, autoimmune, endocrine and psychiatric diseases both before and after index date in patients with PMR. Conversely, the risk of cancer and neurological disease was significantly lower in patients with PMR prior to index date. The risk of all but one glucocorticoid (GC) related adverse event was higher in patients with PMR before and after index date.

Strengths and limitations

This is the largest study investigating the association of PMR with a broad range of relevant comorbidities before and after the diagnosis of PMR. The comorbidities were selected using robust methods, and CPRD is a large database, with over 17 million validated patients who are representative of the UK population. (13) The data in CPRD is collected in the course of routine clinical care, and so reflects the reality of day-to-day primary care. Furthermore, as PMR is managed predominantly in primary care, the CPRD is an ideal way to obtain accurate estimates of the comorbidity burden for people with PMR.

A potential limitation is case ascertainment. Patients were diagnosed with PMR in the presence of a Read code for PMR, and at least two GC prescriptions. This method is well-established in CPRD studies of PMR. (11,14,27) Clinical classification criteria do exist for PMR, (28) however they were designed to create standard populations of patients for research

studies, rather than diagnostic accuracy. Furthermore, due to the lack of specific diagnostic clinical criteria, or a gold standard diagnostic laboratory test, it is established that clinicians find diagnosing PMR a challenge, (9) therefore the inclusion of treatment in the definition of PMR will increase specificity.

The presence of comorbid diagnoses were based on Read codes only. However, previous research has found that the positive predictive value of a CPRD diagnosis is high, particularly for chronic diseases. (29) Another potential limitation is that the wide range of comorbidities examined could increase the risk of finding statistically significant associations by chance. However, we have interpreted our findings in this context. We also performed a sensitivity analysis, in which we ascertained the risk of admission to hospital following diagnosis with PMR, with the primary reason being any of the comorbidities assessed in this study. Reassuring, the results were similar when compared to the main analysis, and are included as supplement S4.

Reporting composite outcomes, such as overall vascular risk, increased the study power, but may inadvertently obscure associations between individual outcomes. Therefore, both composite and individual outcomes were reported.

Furthermore, to strengthen the validity of findings, we used robust standard errors and adjusted the calculated likelihood ratios for several covariates, including age, sex, registered general practice, smoking status, BMI and alcohol consumption. This accounts for the associations between comorbid diagnoses and certain risk factors. For example, it is well established that PMR is more likely to be diagnosed in women. However, women and men have different risk profiles for many conditions. While we stress that the study aim was to assess for possible associations between PMR and other comorbidities, and not to prove

causation, this adjustment for potential confounders helps to understand the relationships more clearly.

Comparison to other studies

The risk of cancer was significantly lower in patients with PMR prior to index date (OR 0.89 [0.86, 0.93]) and not significantly different thereafter (HR 0.98 [0.94, 1.01]). This is consistent with existing literature, which has reported equivocal results. (11,30–34) The reduction in the risk prior to index date may be due to diagnostic overshadowing, wherein previous serious medical conditions reduce the likelihood of other diagnoses being made. Clinical classification criteria for PMR state that cancer should be excluded in patients presenting with suspected PMR. (28,35) Therefore, it may be that people with cancer are less likely to be diagnosed with PMR rather than vice-versa.

Although most of the existing literature suggest that the risk of vascular disease may be higher among patients with PMR, (16,27,36–41) a consensus has not been reached. The two largest studies, both based on results from primary care databases, reported differing outcomes. Hancock et al. found an increase (HR 2.6 [2.4, 2.9]), (27) while Pujades-Rodriguez et al., (16) reported the opposite (incidence rate ratio 0.88 [0.83,0.94]). The current study found an increased risk of vascular disease in patients with PMR, although at a lower magnitude (HR 1.23 [1.19, 1.28]) compared to Hancock et al. Furthermore, a recent study found that PMR shared risk factors with vascular diseases, (42) strengthening the assertion that an association may exist.

Whether PMR is an autoimmune or auto-inflammatory disease remains a matter of debate. (43) However, these results provide more evidence that PMR should be regarded as an

autoimmune condition. Prior to index date, the likelihood of a previous autoimmune diagnosis was significantly increased (OR 1.32 [1.25, 1.39]). After index date this effect was even more pronounced (HR 4.68 [4.35, 5.03]). This is in agreement with previous evidence which demonstrated associations between PMR and Sjogren's disease (OR 5.1), myositis (OR 8.1) and dermatomyositis (OR 12.6). (44) However, as PMR can present with none-specific symptoms, this could have been due to diagnostic confusion. (9)

This study found that the risks of GC related complications were higher in patients with PMR compared to matched controls. This is consistent with previous studies that have demonstrated an increase in the incidence of cataracts (45) and fragility fractures. (15) In the current study, the risk of osteoporosis was greater in patients with PMR although the risk of hip fracture was not significantly different. This could be due to improved prophylactic treatment or as a consequence of the reduction in the risk of diagnosis with PMR in patients with cancer. The increased risk of other GC related comorbidities, such as infections, cataracts and glaucoma were present prior to index date as well, which may reflect the use of GCs prior to formal diagnosis by some clinicians.

No previous estimates of the risk of respiratory and renal diseases in people with PMR exist. From this data, it appears that the risk of renal disease, asthma, lung fibrosis and COPD are significantly higher in patients with PMR both prior to, and following, index date. Despite this, the proportion of patients with PMR who were recorded as smokers was less than the proportion of controls. This may be due to the increased rate of respiratory conditions causing patients to stop smoking, as the most recent status prior to index date was used.

As people with PMR are likely to have regular monitoring as part of their follow up, the increase in the risk of renal disease may be related to surveillance bias, as up to one million people in the UK may have undiagnosed renal disease. (46) The increased risk of diagnosis

with asthma in patients with PMR could be due to shared immunological pathways. Asthma and PMR are both conditions that are characterised by inflammation and responsiveness to GC treatment. (47)

Few studies have assessed the risk of psychiatric conditions in patients with PMR. A recent cohort of 704 patients in the UK with PMR found that 15% of patients reported current depressive symptoms. (48) This study is consistent with this, as the risk of depression and anxiety was higher in patients with PMR. This could be due to the chronic pain and stiffness associated with PMR, as depression is known to be linked to chronic pain. (49) Alternatively, the increased risk of psychiatric conditions may be associated with glucocorticoid use. (50)

Very little evidence xists to ascertain whether PMR is associated with neurological diseases, the current study found that patients with Parkinson's disease, MS and dementia were significantly less likely to be diagnosed with PMR. However, rather than these conditions being protective against PMR, this reduction in risk is more likely to be due to diagnostic overshadowing, wherein patients with these conditions are less likely to receive a diagnosis of PMR.

Many of the previous studies into comorbidities in PMR were conducted in secondary care. This study, a primary care based epidemiological investigation, will therefore include patients with more severe disease who are subsequently referred to secondary care, as well as those whose symptoms are able to be managed without specialist input. As such, it is likely that this study is, overall, likely to include a large proportion of patients with relatively mild disease. This may account for some of the differences observed with previous studies.

Conclusion and clinical and research implications

This study found that patients with PMR have a greater number of comorbidities when compared to matched controls before and after diagnosis.

A number of reasons could be suggested for this. For example, it may be related to the systemic inflammation characteristic of PMR or secondary to the treatment of PMR with glucocorticoids. Some of the excess risk may be due to surveillance bias, but this seems unlikely given associations with many comorbidities were also identified prior to index date. Specifically, the risk of GC related comorbidities was raised in patients with PMR, therefore future research should in part focus on the identification of, and provision of 'steroid-sparing' therapy for, patients at high risk of prolonged GC treatment, or where GC treatment may significantly worsen an existing comorbidity, such as diabetes.

Additionally, the presence of PMR greatly increases a patient's chances of a diagnosis with another autoimmune condition. PMR should therefore be regarded as an immunologically mediated disease.

Conversely, patients with a pre-existing diagnosis of cancer or neurological disease were significantly less likely to be diagnosed with PMR. PMR can be a challenging illness to diagnose and manage, and this study reinforces this in the context of a high level of associated comorbidity before and after diagnosis, including those comorbidities linked with glucocorticoids, the most common treatment for PMR. Additionally current clinical classification criteria advocate a process of exclusion of other causes prior to making a diagnosis of PMR that, while trying to ensure alternative and more serious illnesses are not overlooked, appears to have encouraged the concept of diagnostic overshadowing.

An important area for further research is to ascertain whether the differences observed in levels of comorbidities between patients with PMR and their matched controls translates to

409 an increase in the risk of early mortality. Existing population based studies have so far
410 demonstrated no excess early mortality among patients with PMR. (51)

411 This leads to a risk that some patients with certain pre-existing illnesses may not receive a
412 diagnosis of, and therefore appropriate treatment for, PMR. These patients may then continue
413 to suffer the sometimes debilitating symptoms associated with PMR. Future guidelines
414 therefore need to therefore take into account the high levels of comorbidity in patients with
415 PMR and recognise the impact of these comorbidities on the diagnostic and treatment
416 challenges that PMR poses. Clinicians should be encouraged to consider the possibility of
417 PMR in all older patients that present with pain, stiffness and elevated inflammatory markers,
418 regardless of the existence of other comorbidities.

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Acknowledgements:

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

Financial disclosure statement:

No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No specific funding was received for this study.

RP is funded by NHS Research and Infrastructure funds.
CDM is funded by the National Institute for Health Research (NIHR) Applied Research Collaboration (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 and Social Care. 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.

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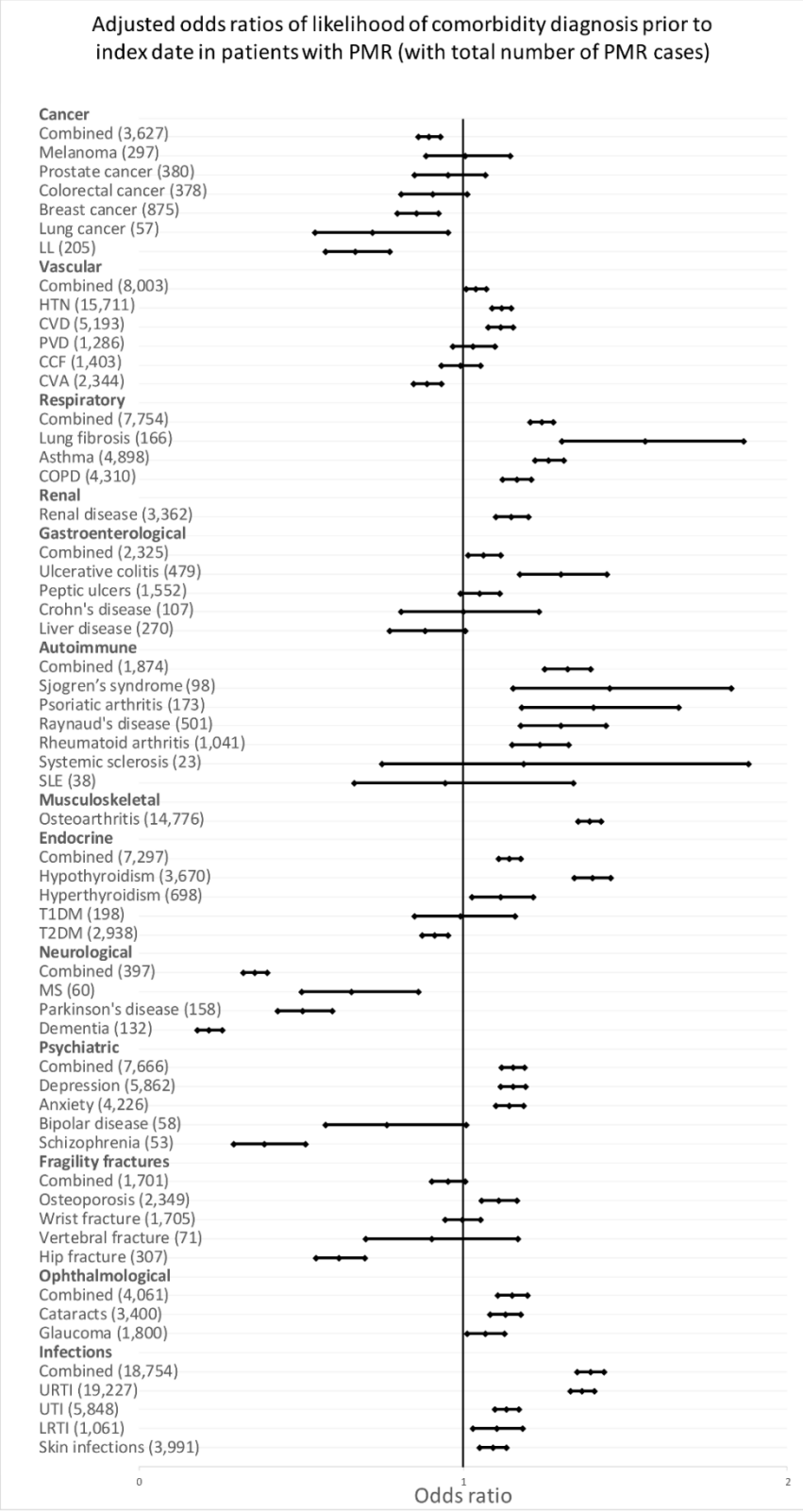


Figure 1: Adjusted odds ratios of likelihood of comorbidity diagnosis prior to index date in patients with PMR (with total number of PMR cases)

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

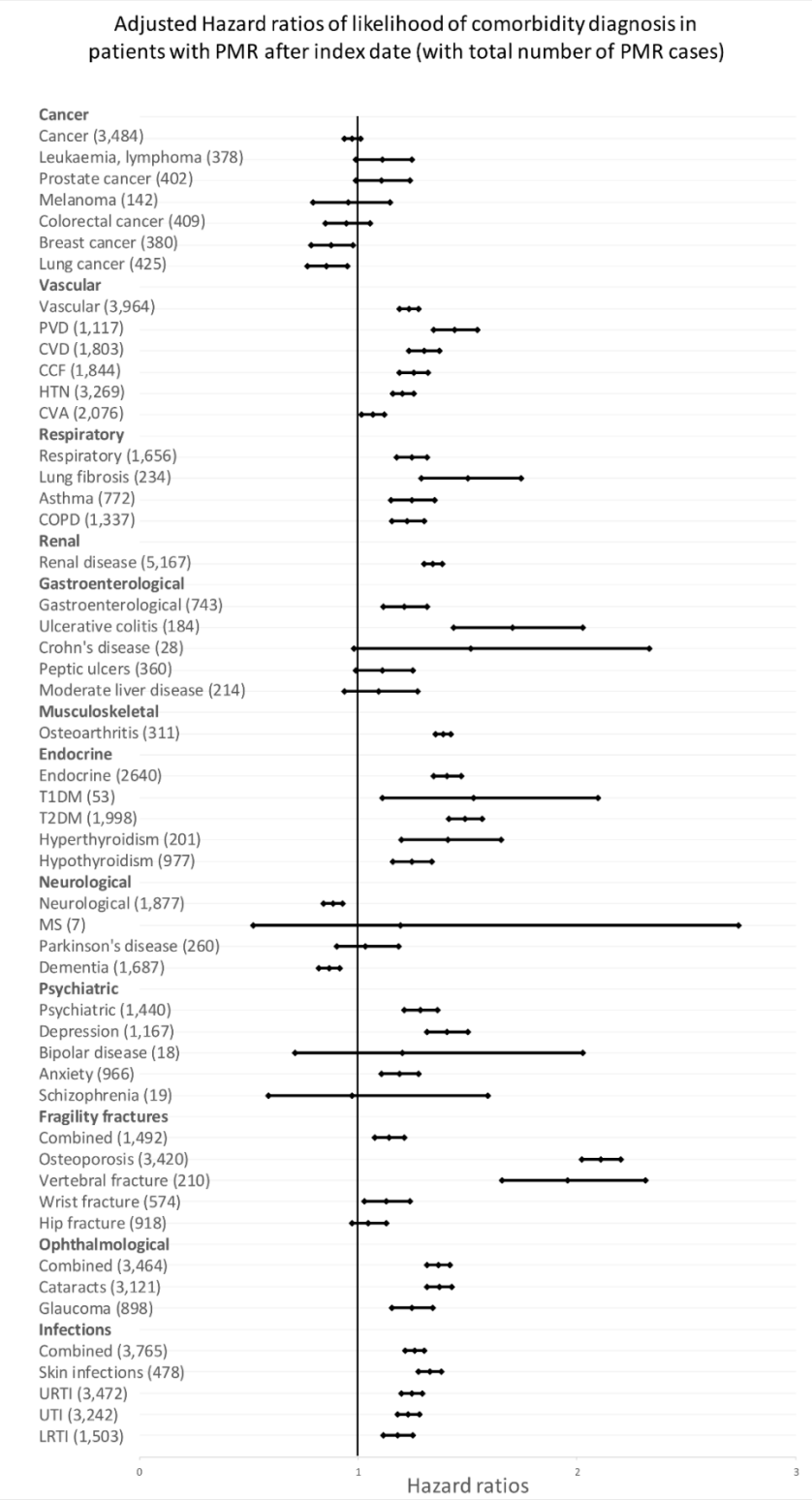


Figure 2: Adjusted hazard ratios of likelihood of comorbidity diagnosis in patients with PMR after index date (with total number of PMR cases)

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

Supplement 1: Final list of individual comorbidities for assessment

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

* Charlson comorbidity index ** Identified during systematic review *** Added following expert review
+ Only used in calculation of Charlson index

Supplement 2: Prevalence of composite and stratified comorbidities in patients with PMR and their controls prior to index date

	Case			Control		
Years prior to index date	**5y**	**2y**	**1y**	**5y**	**2y**	**1y**
Comorbidities						
Cancer	8·0	10·3	11·3	8·5	11·0	12·2
Breast cancer	2·3	2·6	2·7	2·4	3·0	3·2
Prostate cancer	0·6	1·0	1·2	0·7	1·0	1·2
Lung cancer	0·1	0·1	0·2	0·1	0·2	0·2
Colorectal cancer	0·8	1·0	1·2	0·8	1·1	1·3
Melanoma	0·7	0·9	0·9	0·7	0·8	0·9
Leukaemia, lymphoma	0·4	0·6	0·6	0·6	0·8	0·9
Vascular	18·6	23·3	25·0	17·4	21·7	23·3
MI	12·9	15·3	16·2	11·3	13·4	14·1
CCF	2·4	3·8	4·4	2·3	3·6	4·1
PVD	2·7	3·6	4·0	2·6	3·5	3·8
CVD	4·6	6·5	7·3	5·1	7·1	7·8
HTN	40·0	46·7	49·1	37·3	43·0	45·3
Respiratory	20·7	23·1	24·2	17·3	19·3	20·2
Asthma	13·2	14·7	15·3	10·7	11·8	12·3
COPD	10·8	12·6	13·5	9·4	11·0	11·7
Lung fibrosis	0·2	0·4	0·5	0·2	0·3	0·3
Renal disease	4·1	8·4	10·5	3·8	7·4	9·1
Gastroenterological	6·1	6·9	7·3	5·8	6·5	6·8
Moderate liver disease	0·6	0·7	0·8	0·7	0·9	1·0
Peptic ulcers	4·2	4·7	4·9	4·1	4·4	4·6
Crohn's disease	0·3	0·3	0·3	0·3	0·3	0·3
Ulcerative colitis	1·2	1·4	1·5	1·0	1·1	1·1
Autoimmune	4·6	5·4	5·9	3·7	4·2	4·5
SLE	0·1	0·1	0·1	0·1	0·1	0·1
Systemic sclerosis	0·1	0·1	0·1	0·0	0·1	0·1
Rheumatoid arthritis	2·6	3·0	3·3	2·2	2·5	2·6
Sjogren’s syndrome	0·2	0·3	0·3	0·2	0·2	0·2
Psoriatic arthritis	0·4	0·5	0·5	0·3	0·4	0·4
Raynaud's disease	1·1	1·4	1·6	0·9	1·1	1·2
Osteoarthritis	37·6	43·4	46·2	31·5	36·1	38·2
Endocrine	17·9	21·3	22·8	15·8	18·9	20·1
Hyperthyroidism	1·9	2·1	2·2	1·7	1·9	2·0
Hypothyroidism	9·1	10·7	11·5	6·7	8·0	8·5
T1DM	0·5	0·6	0·6	0·5	0·6	0·6
T2DM	6·3	8·4	9·2	6·8	8·8	9·5
Addison's disease	0·0	0·1	0·1	0·0	0·0	0·0
Neurological	0·7	1·0	1·2	1·6	2·7	3·3
Dementia	0·1	0·2	0·4	0·4	1·3	1·8
Parkinson's disease	0·3	0·4	0·5	0·5	0·8	0·9
MS	0·2	0·2	0·2	0·3	0·3	0·3
Psychiatric	21·4	23·1	24·0	19·4	20·9	21·7
Schizophrenia	0·1	0·2	0·2	0·4	0·4	0·4

	Case			Control		
Years prior to index date	**5y**	**2y**	**1y**	**5y**	**2y**	**1y**
Bipolar disease	0·1	0·2	0·2	0·2	0·2	0·2
Depression	16·3	17·6	18·3	14·6	15·8	16·5
Anxiety	11·6	12·6	13·2	10·5	11·4	11·9
Fragility fractures	5·0	5·0	5·3	5·2	5·1	5·5
Osteoporosis	4·5	6·4	7·3	4·1	5·8	6·6
Hip fracture	0·5	0·8	1·0	0·8	1·2	1·5
Wrist fracture	4·5	5·1	5·3	4·5	5·0	5·3
Vertebral fracture	0·1	0·2	0·2	0·2	0·2	0·2
Ophthalmological	9·5	11·3	12·7	8·4	9·8	10·8
Cataracts	6·1	9·3	10·6	5·3	8·0	9·1
Glaucoma	4·0	5·1	5·6	3·7	4·7	5·1
Infections	57·9	56·4	58·6	52·1	49·9	52·1
UTI	14·2	16·9	18·3	12·8	15·1	16·4
URTI	51·4	57·1	60·1	45·1	50·0	52·8
LRTI	2·4	3·0	3·3	2·3	2·7	2·9
Skin infections	8·9	11·2	12·5	8·0	10·2	11·4

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

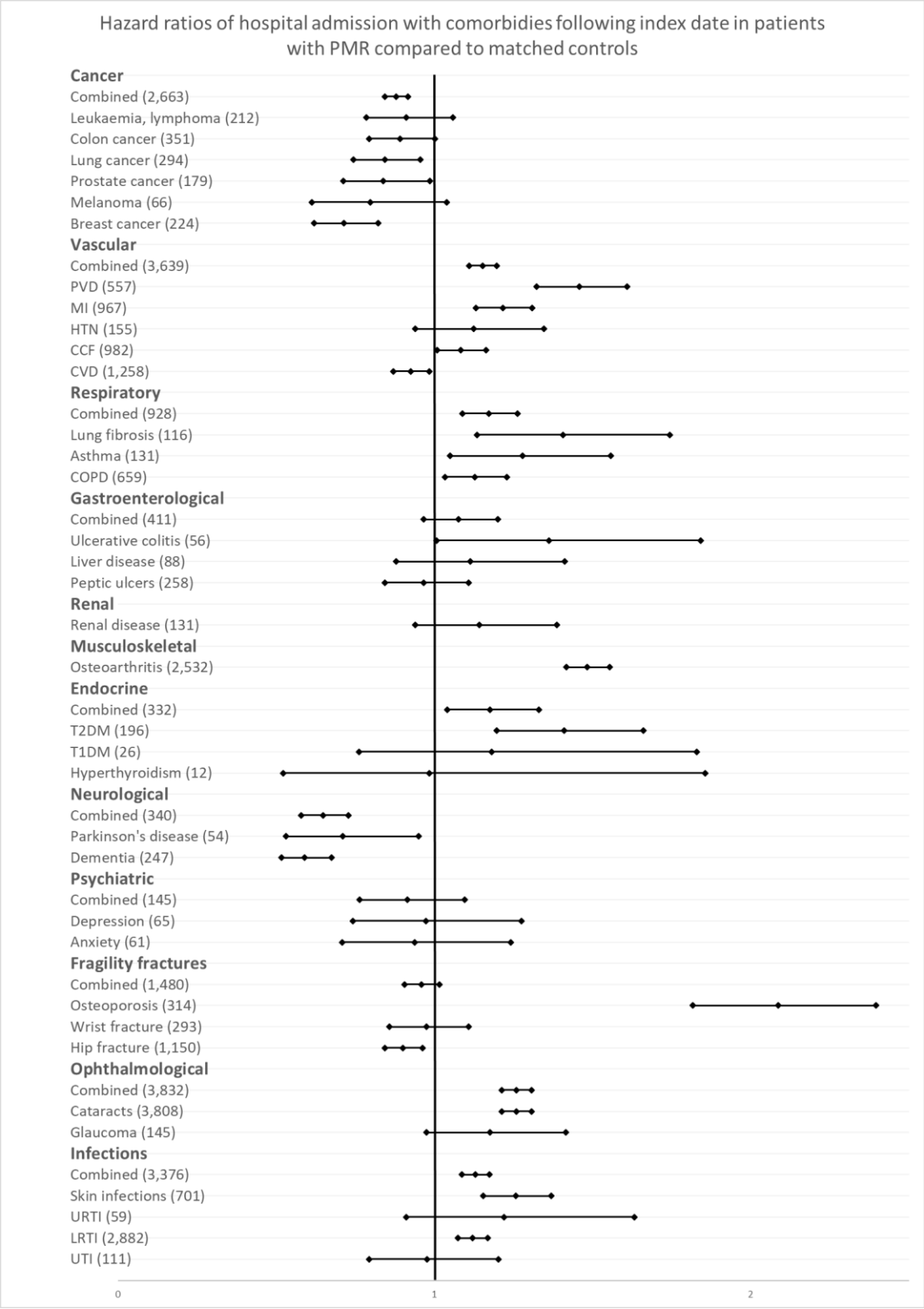
Supplement 3: Likelihood ratios of comorbidities before and after index date

	Prior to index date	**Following index date**
	Adjusted odds ratios	Adjusted hazard ratios
Cancer	0·89 (0·86,0·93)	0·98 (0·94,1·01)
Breast cancer	0·86 (0·80,0·92)	0·88 (0·79, 0·98)
Prostate cancer	0·95 (0·85,1·07)	1·11 (0·99, 1·24)
Lung cancer	0·72 (0·54,0·95)	0·86 (0·77, 0·95)
Colorectal cancer	0·91 (0·81,1·01)	0·95 (0·85, 1·06)
Melanoma	1·01 (0·89,1·14)	0·96 (0·80, 1·15)
Leukaemia, lymphoma	0·67 (0·58,0·77)	1·11 (0·99, 1·25)
Vascular	1·04 (1·01,1·07)	1·23 (1·19,1·28)
MI	1·12 (1·08,1·16)	1·30 (1·24, 1·37)
CCF	0·99 (0·93,1·05)	1·25 (1·19, 1·32)
PVD	1·03 (0·97,1·10)	1·44 (1·35, 1·55)
CVD	0·89 (0·85,0·93)	1·07 (1·02, 1·12)
HTN	1·12 (1·09,1·15)	1·21 (1·16, 1·25)
Respiratory	1·24 (1·21,1·28)	1·25 (1·18,1·32)
Asthma	1·27 (1·22,1·31)	1·25 (1·15, 1·35)
COPD	1·17 (1·12,1·21)	1·23 (1·15, 1·30)
Lung fibrosis	1·56 (1·31,1·87)	1·50 (1·29, 1·75)
Renal disease	1·15 (1·10,1·20)	1·34 (1·30, 1·39)
Gastroenterological	1·06 (1·02,1·12)	1·21 (1·12,1·32)
Moderate liver disease	0·88 (0·77,1·01)	1·09 (0·94, 1·27)
Peptic ulcers	1·05 (0·99,1·11)	1·11 (0·99, 1·25)
Crohn's disease	1·00 (0·81,1·23)	1·52 (0·98, 2·33)
Ulcerative colitis	1·30 (1·18,1·45)	1·71 (1·44, 2·03)
Autoimmune	1·32 (1·25,1·39)	4·68 (4·35,5·03)
SLE	0·94 (0·67,1·34)	4·65 (2·92, 7·40)
Systemic sclerosis	1·19 (0·75,1·88)	2·23 (1·21, 4·14)
Rheumatoid arthritis	1·24 (1·15,1·33)	6·99 (6·35, 7·70)
Sjogren’s syndrome	1·45 (1·16,1·83)	3·07 (2·16, 4·35)
Psoriatic arthritis	1·40 (1·18,1·67)	8·23 (6·46, 10·47)
Raynaud's disease	1·30 (1·18,1·44)	1·47 (1·26, 1·71)
Osteoarthritis	1·39 (1·35,1·43)	1·90 (1·83, 1·97)
Endocrine	1·14 (1·11,1·18)	1·41 (1·35,1·47)
Hyperthyroidism	1·12 (1·03,1·22)	1·41 (1·20, 1·66)
Hypothyroidism	1·40 (1·34,1·46)	1·25 (1·16, 1·34)
T1DM	0·99 (0·85,1·16)	1·53 (1·11, 2·10)
T2DM	0·91 (0·88,0·95)	1·49 (1·42, 1·57)
Addison's disease	1·35 (0·82,2·24)	4·01 (2·48, 6·48)
Neurological	0·36 (0·32,0·40)	0·89 (0·84,0·93)
Dementia	0·22 (0·18,0·26)	0·87 (0·82, 0·92)
Parkinson's disease	0·50 (0·43,0·60)	1·04 (0·90, 1·19)
MS	0·66 (0·50,0·86)	1·20 (0·52, 2·74)
Psychiatric	1·15 (1·12,1·19)	1·29 (1·21,1·36)
Schizophrenia	0·39 (0·29,0·51)	1·20 (0·71, 2·03)
Bipolar disease	0·76 (0·58,1·01)	1·41 (1·32, 1·50)
Depression	1·15 (1·12,1·19)	1·19 (1·11, 1·28)

Anxiety	1·14 (1·10,1·19)	0·97 (0·59, 1·60)
Fragility fractures	0·95 (0·90,1·01)	1·14 (1·08,1·21)
Osteoporosis	1·11 (1·06,1·17)	2·11 (2·03, 2·20)
Hip fracture	0·62 (0·55,0·70)	1·05 (0·98, 1·13)
Wrist fracture	1·00 (0·94,1·05)	1·13 (1·03, 1·24)
Vertebral fracture	0·91 (0·70,1·17)	1·96 (1·66, 2·32)
Ophthalmological	1·15 (1·11,1·20)	1·37 (1·32,1·42)
Cataracts	1·13 (1·08,1·18)	1·37 (1·32, 1·43)
Glaucoma	1·07 (1·01,1·13)	1·25 (1·16, 1·35)
Infections	1·39 (1·35,1·43)	1·26 (1·22,1·31)
UTI	1·14 (1·10,1·17)	1·23 (1·18, 1·28)
URTI	1·37 (1·33,1·41)	1·25 (1·20, 1·29)
LRTI	1·11 (1·03,1·18)	1·18 (1·12, 1·25)
Skin infections	1·09 (1·05,1·13)	1·33 (1·28, 1·38)

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

Supplement 4: Hazard Ratios of admission with comorbidities in patients with PMR vs controls following index date



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

	Cases /exposed								**Controls/unexposed**							
Charlson score	**Pre diagnosis**			**Following diagnosis**					**Pre diagnosis**			**Following diagnosis**				
	5y (26,633)	2y (31,984)	1y (31,984)	At diagnosis (31,984)	1y (28,490)	2y (24,699)	5y (14,738)	10y (4,467)	5y (120,869)	2y (149,436)	1y (149,436)	At diagnosis (149,436)	1y (128,302)	2y (108,197)	5y (60,272)	10y (16,751)
0	13,640 (51.2)	13,952 (43.6)	12,974 (40.6)	11,786 (36.9)	9,448 (33.2)	7,614 (30.8)	3,808 (25.8)	915 (20.5)	65,882 (54.5)	70,405 (47.1)	66,094 (44.2)	61,711 (41.3)	51,101 (39.8)	41,858 (38.7)	21,231 (35.2)	5,090 (30.4)
1	6,718 (25.2)	7,953 (24.9)	7,776 (24.3)	7,568 (23.7)	6,593 (23.1)	5,603 (22.7)	3,147 (21.4)	860 (19.3)	27,607 (22.8)	33,699 (22.6)	33,216 (22.2)	32,431 (21.7)	27,376 (21.3)	22,699 (21.0)	12,153 (20.2)	3,286 (19.6)
2	3,667 (13.8)	5,125 (16.0)	5,421 (16.9)	5,732 (17.9)	5,319 (18.7)	4,668 (18.9)	2,846 (19.3)	854 (19.1)	15,716 (13.0)	23,278 (15.6)	24,431 (16.3)	25,398 (17.0)	22,352 (17.4)	19,115 (17.7)	10,995 (18.2)	3,114 (18.6)
3	1,595 (6.0)	2,650 (8.3)	2,979 (9.3)	3,369 (10.5)	3,306 (11.6)	3,102 (12.6)	2,111 (14.3)	725 (16.2)	6,959 (5.8)	11,631 (7.8)	12,974 (8.7)	14,319 (9.6)	12,859 (10.0)	11,318 (10.5)	6,980 (11.6)	2,202 (13.1)
≥4	1,013 (3.8)	2,304 (7.2)	2,834 (8.9)	3,529 (11)	3,824 (13.4)	3,712 (15.0)	2,826 (19.2)	1,113 (24.9)	4,705 (3.9)	10,423 (7.0)	12,721 (8.5)	15,577 (10.4)	14,614 (11.4)	13,207 (12.2)	8,913 (14.8)	3,059 (18.3)

Table 1: Charlson Comorbidity Index scores in patients with PMR compared to matched controls before and after index date

	Cases					Controls				
	At diagnosis	**Up to one year**	**Up to two years**	**Up to five years**	**Up to ten years**	**At diagnosis**	**Up to one year**	**Up to two years**	**Up to five years**	**Up to ten years**
Cancer	15.4 (15.0,15.8)	17.2 (16.8,17.6)	22.7 (22.2,23.2)	30.6 (29.9,31.3)	40.1 (38.9,41.3)	16.4 (16.2,16.6)	18.3 (18.1,18.5)	23.8 (23.6,24.1)	31.8 (31.5,32.1)	41.3 (40.7,41.9)
Breast cancer	3.2 (3.0,3.4)	3.4 (3.2,3.6)	4.1 (3.9,4.3)	5.2 (4.9,5.5)	6.6 (6.1,7.2)	3.9 (3.8,4.0)	4.1 (4.0,4.2)	4.9 (4.8,5.0)	6.0 (5.8,6.1)	7.5 (7.2,7.8)
Prostate cancer	2.0 (1.8,2.2)	2.2 (2.0,2.4)	2.8 (2.6,3.0)	3.6 (3.4,3.9)	4.7 (4.2,5.2)	1.7 (1.6,1.7)	1.9 (1.8,1.9)	2.4 (2.3,2.5)	3.3 (3.2,3.5)	4.6 (4.3,4.8)
Lung cancer	0.6 (0.5,0.7)	0.9 (0.8,1.0)	1.5 (1.3,1.6)	2.5 (2.2,2.7)	3.6 (3.2,4.2)	0.7 (0.7,0.7)	1.0 (1.0,1.1)	1.9 (1.8,1.9)	3.0 (2.9,3.2)	4.5 (4.2,4.8)
Colorectal cancer	1.6 (1.5,1.7)	1.8 (1.7,2.0)	2.5 (2.4,2.7)	3.6 (3.3,3.9)	5.2 (4.6,5.8)	1.8 (1.7,1.8)	2.0 (1.9,2.1)	2.7 (2.6,2.8)	3.9 (3.7,4.0)	5.2 (5.0,5.5)
Melanoma	1.1 (1.0,1.2)	1.2 (1.1,1.4)	1.5 (1.3,1.6)	1.8 (1.6,2.0)	2.1 (1.9,2.5)	1.1 (1.1,1.2)	1.2 (1.1,1.3)	1.5 (1.4,1.5)	1.8 (1.7,1.9)	2.4 (2.2,2.5)
LL	1.2 (1.1,1.3)	1.4 (1.2,1.5)	2.0 (1.8,2.1)	2.7 (2.5,3.0)	4.0 (3.5,4.5)	1.3 (1.3,1.4)	1.5 (1.4,1.6)	2.1 (2.0,2.2)	3.0 (2.9,3.1)	4.0 (3.7,4.2)
Vascular	30.5 (29.9,31.0)	32.7 (32.2,33.2)	38.9 (38.4,39.5)	47.7 (47.0,48.4)	57.5 (56.3,58.6)	28.2 (28.0,28.4)	30.0 (29.7,30.2)	35.1 (34.9,35.4)	42.8 (42.5,43.2)	51.5 (50.9,52.1)
MI	18.9 (18.5,19.4)	20.0 (19.6,20.5)	23.1 (22.6,23.6)	27.2 (26.6,27.8)	32.5 (31.4,33.5)	16.6 (16.4,16.8)	17.4 (17.2,17.6)	19.8 (19.5,20.0)	23.1 (22.8,23.4)	27.5 (27.0,28.0)
CCF	6.6 (6.3,6.8)	7.6 (7.3,7.9)	10.5 (10.1,10.8)	15.1 (14.6,15.7)	20.9 (19.8,21.9)	5.9 (5.8,6.1)	6.7 (6.6,6.8)	9.0 (8.9,9.2)	12.7 (12.5,13.0)	17.8 (17.3,18.3)
PVD	5.5 (5.3,5.8)	6.2 (5.9,6.5)	7.9 (7.5,8.2)	10.9 (10.4,11.4)	14.5 (13.7,15.4)	5.0 (4.9,5.1)	5.4 (5.3,5.5)	6.7 (6.6,6.8)	8.7 (8.5,8.9)	10.6 (10.3,11.0)
CVD	9.9 (9.6,10.2)	10.9 (10.6,11.3)	14.4 (14.0,14.8)	19.8 (19.2,20.4)	27.0 (25.9,28.1)	10.3 (10.2,10.5)	11.3 (11.2,11.5)	14.4 (14.2,14.6)	19.3 (19.0,19.6)	25.3 (24.7,25.8)
HTN	55.4 (54.9,56.0)	57.6 (57.1,58.2)	62.6 (62.0,63.1)	68.9 (68.2,69.5)	74.2 (73.2,75.1)	51.0 (50.7,51.2)	52.8 (52.5,53.0)	57.6 (57.4,57.9)	63.8 (63.4,64.1)	69.8 (69.3,70.3)
Respiratory	27.5 (27.0,28.0)	28.5 (28.0,29.0)	31.1 (30.5,31.6)	34.8 (34.2,35.4)	39.5 (38.5,40.5)	23.2 (23.0,23.4)	24.0 (23.8,24.3)	26.4 (26.1,26.6)	29.6 (29.3,29.8)	33.2 (32.7,33.7)
Asthma	17.0 (16.6,17.5)	17.5 (17.1,17.9)	18.9 (18.5,19.4)	20.6 (20.1,21.1)	23.1 (22.3,23.9)	14.0 (13.8,14.2)	14.4 (14.2,14.6)	15.5 (15.3,15.7)	16.8 (16.6,17.1)	18.4 (18.0,18.7)
COPD	16.0 (15.6,16.4)	16.8 (16.4,17.2)	18.9 (18.4,19.4)	22.1 (21.5,22.6)	25.3 (24.5,26.2)	14.0 (13.8,14.1)	14.7 (14.5,14.8)	16.5 (16.3,16.7)	19.1 (18.9,19.4)	22.1 (21.7,22.5)
Lung fibrosis	0.9 (0.8,1.0)	1.0 (0.9,1.1)	1.3 (1.2,1.4)	1.9 (1.7,2.2)	2.7 (2.3,3.1)	0.5 (0.5,0.5)	0.6 (0.5,0.6)	0.8 (0.8,0.9)	1.3 (1.2,1.4)	1.7 (1.5,1.8)
Renal disease	16.9 (16.5,17.4)	20.1 (19.6,20.5)	28.3 (27.8,28.9)	39.8 (39.0,40.5)	52.3 (51.1,53.6)	14.0 (13.8,14.2)	16.1 (15.9,16.3)	22.6 (22.4,22.9)	32.1 (31.7,32.4)	42.7 (42.0,43.3)
Gastroenterological	8.6 (8.3,8.9)	9.0 (8.7,9.3)	10.2 (9.9,10.6)	12.1 (11.7,12.5)	14.5 (13.7,15.2)	7.9 (7.8,8.1)	8.3 (8.1,8.4)	9.3 (9.2,9.5)	10.9 (10.7,11.1)	12.6 (12.2,12.9)
Moderate liver disease	1.2 (1.1,1.3)	1.3 (1.2,1.4)	1.7 (1.5,1.9)	2.2 (2.0,2.4)	2.9 (2.5,3.4)	1.2 (1.2,1.3)	1.3 (1.3,1.4)	1.7 (1.6,1.8)	2.2 (2.1,2.3)	2.7 (2.6,2.9)
Peptic ulcers	5.6 (5.3,5.9)	5.8 (5.5,6.0)	6.4 (6.1,6.7)	7.3 (7.0,7.7)	8.6 (8.0,9.1)	5.2 (5.1,5.4)	5.4 (5.3,5.6)	6.0 (5.8,6.1)	6.8 (6.6,6.9)	7.8 (7.5,8.1)
Crohn's disease	0.4 (0.3,0.5)	0.4 (0.3,0.5)	0.5 (0.4,0.5)	0.5 (0.4,0.6)	0.6 (0.5,0.8)	0.4 (0.4,0.4)	0.4 (0.4,0.4)	0.4 (0.4,0.5)	0.5 (0.4,0.5)	0.5 (0.5,0.6)
Ulcerative colitis	1.8 (1.7,2.0)	2.0 (1.8,2.1)	2.2 (2.1,2.4)	2.6 (2.4,2.9)	3.1 (2.8,3.5)	1.3 (1.3,1.4)	1.4 (1.4,1.5)	1.6 (1.5,1.7)	1.9 (1.8,2.0)	2.1 (2.0,2.3)
Autoimmune	9.6 (9.2,9.9)	10.6 (10.3,11.0)	12.6 (12.2,13.0)	15.0 (14.5,15.5)	17.4 (16.7,18.2)	5.2 (5.1,5.4)	5.4 (5.3,5.6)	6.0 (5.9,6.2)	7.0 (6.8,7.1)	7.9 (7.7,8.2)
SLE	0.2 (0.1,0.2)	0.2 (0.2,0.3)	0.3 (0.2,0.3)	0.3 (0.3,0.4)	0.4 (0.3,0.5)	0.2 (0.1,0.2)	0.2 (0.1,0.2)	0.2 (0.2,0.2)	0.2 (0.2,0.2)	0.2 (0.2,0.2)
Systemic sclerosis	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.2)	0.2 (0.1,0.2)	0.3 (0.1,0.4)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.2 (0.1,0.2)
Rheumatoid arthritis	6.1 (5.8,6.4)	6.8 (6.5,7.1)	8.2 (7.9,8.5)	9.7 (9.3,10.1)	11.5 (10.9,12.2)	3.0 (3.0,3.1)	3.1 (3.1,3.2)	3.5 (3.4,3.6)	3.9 (3.7,4.0)	4.3 (4.1,4.5)
Sjogren’s syndrome	0.4 (0.3,0.5)	0.4 (0.4,0.5)	0.6 (0.5,0.6)	0.6 (0.5,0.7)	0.8 (0.6,1.1)	0.3 (0.2,0.3)	0.3 (0.2,0.3)	0.3 (0.3,0.3)	0.3 (0.3,0.4)	0.4 (0.3,0.4)
Psoriatic arthritis	0.9 (0.8,1.0)	1.1 (0.9,1.2)	1.3 (1.2,1.5)	1.7 (1.5,1.9)	2.0 (1.7,2.3)	0.5 (0.4,0.5)	0.5 (0.4,0.5)	0.5 (0.5,0.5)	0.6 (0.5,0.6)	0.6 (0.6,0.7)
Raynaud's disease	1.9 (1.8,2.1)	2.1 (1.9,2.2)	2.4 (2.3,2.6)	3.1 (2.9,3.4)	3.7 (3.3,4.1)	1.5 (1.4,1.5)	1.6 (1.5,1.6)	1.8 (1.7,1.9)	2.2 (2.1,2.3)	2.7 (2.5,2.9)
Osteoarthritis	58.6 (58.0,59.1)	61.4 (60.9,62.0)	67.3 (66.7,67.8)	73.3 (72.7,73.9)	78.6 (77.6,79.5)	43.5 (43.2,43.8)	45.2 (44.9,45.4)	49.7 (49.4,50.0)	55.7 (55.4,56.1)	61.3 (60.8,61.9)
Endocrine	28.2 (27.7,28.7)	29.7 (29.2,30.2)	33.6 (33.1,34.2)	38.9 (38.3,39.6)	45.0 (43.9,46.1)	23.8 (23.5,24.0)	24.9 (24.6,25.1)	28.1 (27.8,28.3)	33.0 (32.7,33.3)	38.0 (37.5,38.5)
Hyperthyroidism	2.6 (2.4,2.8)	2.7 (2.5,2.9)	3.1 (2.9,3.3)	3.6 (3.3,3.8)	4.0 (3.6,4.4)	2.3 (2.2,2.4)	2.4 (2.3,2.5)	2.6 (2.5,2.7)	3.0 (2.9,3.1)	3.5 (3.3,3.6)
Hypothyroidism	13.8 (13.4,14.2)	14.3 (13.9,14.7)	15.9 (15.5,16.4)	18.4 (17.9,18.9)	21.4 (20.6,22.3)	10.1 (9.9,10.2)	10.5 (10.4,10.7)	11.9 (11.7,12.1)	14.1 (13.8,14.3)	16.4 (16.0,16.8)
T1DM	0.8 (0.7,0.9)	0.8 (0.7,0.9)	0.9 (0.8,1.0)	1.0 (0.8,1.1)	1.0 (0.9,1.2)	0.7 (0.7,0.8)	0.7 (0.7,0.8)	0.8 (0.7,0.8)	0.9 (0.8,0.9)	0.9 (0.9,1.0)

	Cases					Controls				
	At diagnosis	**Up to one year**	**Up to two years**	**Up to five years**	**Up to ten years**	**At diagnosis**	**Up to one year**	**Up to two years**	**Up to five years**	**Up to ten years**
T2DM	12.9 (12.6,13.3)	14.1 (13.7,14.4)	16.9 (16.5,17.4)	20.8 (20.2,21.4)	25.3 (24.4,26.3)	11.8 (11.7,12.0)	12.6 (12.4,12.7)	14.8 (14.6,15.0)	18.2 (18.0,18.5)	21.9 (21.4,22.3)
Addison's disease	0.1 (0.1,0.1)	0.1 (0.1,0.2)	0.2 (0.1,0.2)	0.3 (0.2,0.4)	0.3 (0.2,0.4)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.1 (0.1,0.2)
Neurological	2.5 (2.3,2.6)	3.3 (3.1,3.5)	6.2 (5.9,6.5)	12.3 (11.8,12.9)	21.2 (20.1,22.5)	5.3 (5.2,5.4)	6.2 (6.0,6.3)	9.2 (9.0,9.3)	14.6 (14.4,14.9)	23.4 (22.8,24.0)
Dementia	1.4 (1.2,1.5)	2.0 (1.9,2.2)	4.6 (4.4,4.9)	10.3 (9.8,10.9)	19.1 (18.0,20.4)	3.4 (3.3,3.5)	4.2 (4.1,4.3)	7.0 (6.8,7.1)	12.1 (11.8,12.4)	20.5 (19.9,21.1)
Parkinson's disease	0.8 (0.7,0.9)	0.9 (0.8,1.0)	1.4 (1.3,1.5)	2.0 (1.8,2.3)	2.9 (2.5,3.4)	1.3 (1.2,1.4)	1.4 (1.4,1.5)	1.8 (1.8,1.9)	2.5 (2.4,2.6)	3.3 (3.1,3.5)
MS	0.2 (0.2,0.3)	0.2 (0.2,0.3)	0.2 (0.2,0.3)	0.2 (0.2,0.3)	0.3 (0.2,0.4)	0.3 (0.3,0.4)	0.4 (0.3,0.4)	0.4 (0.3,0.4)	0.4 (0.3,0.4)	0.4 (0.3,0.4)
Psychiatric	27.0 (26.5,27.5)	27.9 (27.4,28.4)	30.3 (29.8,30.8)	33.5 (32.9,34.1)	36.9 (36.0,37.9)	24.5 (24.3,24.8)	25.2 (25.0,25.5)	27.2 (26.9,27.4)	29.8 (29.5,30.1)	32.9 (32.5,33.4)
Schizophrenia	0.2 (0.2,0.2)	0.2 (0.2,0.3)	0.2 (0.2,0.3)	0.3 (0.2,0.4)	0.4 (0.3,0.6)	0.5 (0.5,0.5)	0.5 (0.5,0.6)	0.6 (0.5,0.6)	0.6 (0.5,0.6)	0.6 (0.6,0.7)
Bipolar disease	0.2 (0.2,0.3)	0.2 (0.2,0.3)	0.2 (0.2,0.3)	0.3 (0.2,0.4)	0.3 (0.2,0.4)	0.3 (0.3,0.3)	0.3 (0.3,0.3)	0.3 (0.3,0.4)	0.4 (0.3,0.4)	0.4 (0.3,0.5)
Depression	20.8 (20.4,21.3)	21.6 (21.2,22.1)	23.6 (23.1,24.1)	26.1 (25.6,26.7)	28.8 (27.9,29.6)	18.7 (18.5,18.9)	19.2 (19.0,19.5)	20.7 (20.5,20.9)	22.6 (22.4,22.9)	24.7 (24.3,25.0)
Anxiety	15.1 (14.7,15.5)	15.6 (15.2,16.0)	17.3 (16.9,17.8)	19.8 (19.3,20.4)	22.7 (21.9,23.6)	13.8 (13.6,14.0)	14.2 (14.1,14.4)	15.6 (15.4,15.8)	17.6 (17.3,17.8)	20.2 (19.8,20.6)
Fragility fractures	17.9 (17.5,18.3)	20.4 (19.9,20.8)	25.6 (25.1,26.2)	33.1 (32.4,33.8)	41.5 (40.3,42.7)	14.9 (14.7,15.1)	16.1 (15.9,16.3)	19.7 (19.5,20.0)	25.7 (25.4,26.0)	34.0 (33.4,34.6)
Osteoporosis	12.6 (12.3,13.0)	15.0 (14.6,15.4)	19.6 (19.1,20.1)	25.7 (25.1,26.4)	32.9 (31.7,34.1)	8.8 (8.7,9.0)	9.7 (9.6,9.9)	12.6 (12.4,12.8)	17.4 (17.1,17.7)	24.3 (23.7,24.8)
Hip fracture	1.7 (1.5,1.8)	2.1 (1.9,2.3)	3.4 (3.2,3.7)	6.3 (6.0,6.8)	11.4 (10.5,12.4)	2.3 (2.2,2.3)	2.7 (2.6,2.8)	4.0 (3.9,4.1)	6.5 (6.3,6.7)	10.6 (10.1,11.0)
Wrist fracture	6.3 (6.0,6.6)	6.6 (6.3,6.9)	7.4 (7.1,7.8)	9.2 (8.8,9.6)	11.3 (10.6,12.0)	6.2 (6.1,6.3)	6.5 (6.3,6.6)	7.4 (7.2,7.5)	8.7 (8.5,8.9)	10.8 (10.5,11.2)
Vertebral fracture	0.4 (0.3,0.5)	0.5 (0.4,0.6)	0.9 (0.8,1.0)	1.4 (1.2,1.6)	2.2 (1.9,2.7)	0.4 (0.3,0.4)	0.4 (0.4,0.4)	0.5 (0.5,0.6)	0.9 (0.8,0.9)	1.6 (1.4,1.8)
Ophthalmological	19.5 (19.1,20.0)	21.9 (21.4,22.4)	27.6 (27.1,28.1)	34.8 (34.2,35.5)	43.8 (42.6,45.0)	16.8 (16.6,17.0)	18.3 (18.1,18.5)	22.6 (22.4,22.9)	29.2 (28.9,29.5)	36.5 (35.9,37.1)
Cataracts	14.5 (14.1,14.9)	16.6 (16.2,17.0)	21.7 (21.2,22.2)	28.6 (28.0,29.3)	37.4 (36.2,38.7)	12.3 (12.1,12.4)	13.6 (13.4,13.7)	17.4 (17.2,17.6)	23.3 (23.0,23.6)	30.1 (29.6,30.7)
Glaucoma	7.0 (6.7,7.3)	7.6 (7.4,8.0)	9.2 (8.8,9.5)	11.1 (10.7,11.6)	13.4 (12.7,14.1)	6.3 (6.2,6.4)	6.7 (6.6,6.8)	7.9 (7.7,8.0)	9.9 (9.7,10.1)	12.1 (11.7,12.5)
Infections	74.5 (74.0,75.0)	77.0 (76.6,77.5)	82.6 (82.1,83.0)	88.3 (87.9,88.8)	92.2 (91.5,92.8)	68.0 (67.7,68.2)	70.4 (70.1,70.6)	76.1 (75.9,76.4)	82.6 (82.3,82.8)	88.0 (87.6,88.4)
UTI	22.8 (22.3,23.3)	24.6 (24.1,25.1)	29.4 (28.8,29.9)	37.2 (36.5,37.9)	46.9 (45.7,48.2)	20.3 (20.0,20.5)	21.7 (21.5,21.9)	25.9 (25.7,26.2)	32.5 (32.2,32.8)	40.6 (40.0,41.2)
URTI	66.9 (66.4,67.5)	69.2 (68.7,69.7)	74.5 (74.0,75.0)	80.3 (79.7,80.8)	85.0 (84.2,85.8)	59.6 (59.3,59.8)	61.7 (61.5,62.0)	67.1 (66.8,67.3)	73.3 (73.0,73.6)	79.3 (78.8,79.7)
LRTI	4.7 (4.5,4.9)	5.4 (5.1,5.6)	7.6 (7.3,8.0)	12.2 (11.7,12.7)	18.8 (17.8,19.9)	4.1 (4.0,4.2)	4.7 (4.6,4.8)	6.7 (6.6,6.9)	10.1 (9.8,10.3)	15.2 (14.7,15.7)
Skin infections	16.4 (16.0,16.9)	18.5 (18.1,18.9)	23.5 (23.0,24.0)	31.3 (30.7,32.0)	40.3 (39.1,41.6)	14.7 (14.6,14.9)	16.1 (15.9,16.3)	20.1 (19.8,20.3)	26.4 (26.1,26.7)	34.4 (33.8,35.0)

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

Table 1: Cumulative probability of comorbid diagnosis, with 95% confidence intervals, after index date

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

Table 1: Demographic information of patients included in the study