THE EPIDEMIOLOGY OF POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS.

Max Yates BSc (Hons), MBBS, MSc, MRCP (London)

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University of East Anglia

Norwich Medical School

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ABSTRACT

Introduction

The epidemiology of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) is poorly characterised, with little known about the aetiological factors involved in disease onset and progression. This project aimed to determine the incidence and prevalence of PMR and GCA, including their related morbidity, and to investigate aetiological hypotheses for disease onset and progression using community-based populations and contemporary classification criteria.

Methods

Three large phenotypically informative datasets were constructed: GCANS (n = 4,728), EPIC-Norfolk (n = 25,660) and DCVAS (n = 712) to establish the descriptive epidemiology and investigate aetiological hypotheses centred on cardiovascular risk factors in cross-sectional and longitudinal study designs. The EPIC cohort included unique data from retinal photographs, allowing the application of vasculometric analysis.

Results

The prevalence ranged from 0.91% to 1.62% for PMR and 0.25% to 0.47% for GCA. Age and traditional cardiovascular risk factors were important for both disease onset with associations between hypertension and LDL with PMR. Visual impairment developed in 8% of GCA cases with six months of onset; risk factors for blindness in GCA included peripheral vascular disease. Inflammatory arthritis developed in 10% of PMR cases at 10 years with greatest risk in smokers. Analysis of retinal photographs showed an association between venular width and PMR, but no other characteristic morphological features were identified.

Conclusions

These are the first estimates of PMR and GCA incidence and prevalence for the UK to apply current classification criteria. This is the first study to use a prospective design to show traditional cardiovascular risk factors to be important for disease onset and progression; their presence may point towards a need for more careful monitoring. The novel vasculometric data from retinal photographs provides insight into aetiological hypotheses of disease, particularly those with underlying vascular dysregulation mechanisms, and may be of potential value in screening.

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

DEDICATION

For Jocelyn, Oliver and Beatrice.

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STATEMENT OF PERSONAL CONTRIBUTION

The body of work included in this thesis was completed during my time out of clinical training as a rheumatologist. This was made possible with funding from Arthritis Research UK in the form of a Clinical Research Fellowship.

My personal contribution has been to firstly, design, set-up, and gain ethical approval, and conduct the community-based study to produce prevalence estimates for PMR and GCA from a single large primary care practice (GCANS).

Secondly, establish linking of clinical data to that of the EPIC-Norfolk participants with the aim of extending the phenotype of those individuals with polymyalgia rheumatica and giant cell arteritis.

Thirdly, I was responsible for defining cases of GCA from a large international cohort of patients with vasculitis (DCAVS). I was responsible for the overall analytical approaches used.

Finally I conducted the statistical analyses using the statistical package STATA and was solely responsible for the methods used and confirm that the work presented in this thesis is my own.

ABBREVIATIONS

ACR	American College of Rheumatology
AION	Anterior ischaemic optic neuropathy
BP	Blood pressure
BSR	British Society for Rheumatology
95% CI	95% Confidence interval
CIF	Cumulative incidence function
CPRD	Clinical research datalink
CRAO	Central retinal artery occlusion
CRP	C-reactive protein
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
EPIC	European prospective investigation into cancer and nutrition.
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
$^{18F-}$FDG-PET	18-fluorodexoyglucose positron emission tomography
GCA	Giant cell arteritis
GWAS	Genome wide association studies
HDL	High-density lipoprotein
HIS	Hue, Saturation, Intensity
HLA	Human leukocyte antigen
HR	Hazard ratio
hs-CRP	High-sensitivity CRP

LDL	Low-density lipoprotein
MHC	Major histocompatibility complex
OR	Odds ratio
PION	Posterior optic neuropathy
PMR	Polymyalgia Rheumatica
PVD	Peripheral vascular disease
RGB	Red, Green, Blue
RR	Risk ratio
SD	Standard deviation
SHR	Sub-hazard ratio
THIN	The Health Improvement Network

GLOSSARY

Definitions of any term specific to the thesis, including abbreviations are given below.

CIF	Cumulative incidence function is the probability that the outcome or event is observed before a specified time point.
Competing risk	When individuals are at risk of multiple outcomes.
Cox Regression	Cox proportional hazard model a form of 'survival' model or 'time-to-event' model in which time is divided into infinitesimal bands or clicks. It models the hazard ratio as a function of covariates and although the individual and baseline hazards may change with time they are assumed to be proportional between groups to one another at all times.
Enrolment period	The length of time that recruitment to a cohort study is open to new participants.

HR	The hazard ratio is the ratio of the hazard function evaluated at two values of an explanatory variable.
Incidence	Rate of new disease development during a defined period of time. Usually expressed as either an incidence rate i.e. number of new cases per unit of time or as cumulative incidence, also referred as the incidence proportion, number of new cases occurring over a defined period and is a risk rather than rate of disease.
Incidence density	A measure of incidence rate, also referred to as person-time incidence rate, where number of new cases are defined by the person years at risk (i.e. the total time contributed to follow-up by people who are at risk of disease) and takes account of death and differences in follow-up time particularly useful if there is a long enrolment period.
Kaplan Meier	An estimate of the survival function which is the product of conditional survival to each time at which an event occurs.

Left censoring	When the precise date of the event of interest (disease onset or outcome) is unknown and may predate the start of follow-up.
Lexis expansion	Used in survival function estimation. Periods of time are split so that each record contains the follow-up on one subject through one time band (each observation is expanded into several observations based on the interval of follow-up time). Time can be defined by calendar time in order to create age bands.
Logistic regression	A statistical model used to assess the dependence of a binary outcome (e.g. disease present or absent) on a number of explanatory factors. The probability (p) of one of the outcome states is expressed in the form of logit, $\log_e (p / (1-p))$, which is assumed to be predicted by the linear combination (weighted sum) of the explanatory factors.
OR	The odds ratio is the ratio of two odds, where odds are the chances in favour of the event. The odds is defined as p / 1 - p, where p is the probability, e.g. with a probability of 20% the odds are ¼.

Prevalence	The proportion of individuals with a given disease from a defined population. Usually expressed as either point prevalence (frequency of disease at a given point in time) or period prevalence (frequency of disease at the end of a time period even if time of disease onset was prior to the start of the observation period).
Right censoring	When the outcome of an individual is unknown due to loss of follow-up or alternatively if a participants survives to the end of follow-up their time of death is right censored due to administrative censoring.
Regression	A model for predicting one variable from the value of a set of other variables.
RR	The risk ratio, or relative risk is the probability of the outcome associated with a one unit increase in the risk factor relative to that calculated without such an increase.
SHR	Sub-hazard ratio or more formally the hazard of the subdistribution: a hazard ratio accounting for a competing risk of the outcome of interest. The subhazard ratio is the ratio of

	the subhazard function evaluated at two different values of the covariates.
Stratified model	A survival model which constrains the regression coefficients to be equal across stratum bands of the stratified variable but allows other covariates to vary across the strata.
Wald test	The Wald test is a parametric statistical test used, for example, in logistic regression to determine whether the predictor variable is significantly associated with the outcome against the null. The Wald statistic follows an approximate chi-squared distribution.

PUBLICATIONS

Work included in this thesis appears in the following publications:

Original articles

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PRIZES

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CHAPTER 1 INTRODUCTION

1.0 SUMMARY

This thesis considers the epidemiology of two overlapping conditions that affect older people – Polymyalgia rheumatica (PMR) and Giant Cell Arteritis (GCA), the descriptive epidemiology and aetiology for disease onset and progression are investigated. This chapter gives a brief introduction to PMR and GCA and the importance of these two conditions in which the treatment approaches have changed little since the 1960s, the context for the present work is outlined.

1.1.0 PMR and GCA: overlapping diseases with significant morbidity

Polymyalgia rheumatica (PMR) is an inflammatory condition of unknown aetiology, causing shoulder and hip girdle pain and stiffness (1) while Giant cell arteritis (GCA) is a form of vasculitis predominantly affecting medium and large arteries and has substantial morbidity (2). PMR and GCA are often considered to be part of same disease spectrum (3-5). PMR and GCA often coexist, with 40-60% of patients with GCA having symptoms of PMR. Following temporal artery biopsy, up to 21% of patients with isolated PMR have been reported to show findings consistent with GCA (6). In addition, patients with PMR have been seen to have increased uptake within the subclavian vessels indicative of

undetected large vessel vasculitis, as assessed by 18F-fluorodeoxyglucose positron emission tomography (^{18F}-FDG-PET) (7, 8).

Difficulty in characterisation of these diseases is not limited to distinguishing between them but also extends to recognising their relationship with other diagnoses. They are difficult to diagnose not least due to the lack of a single specific diagnostic test. In the United States it is estimated that accuracy of a family physician diagnosis of PMR is 24% (9) with 40% of cases managed exclusively in the community (10). In the UK PMR is most often diagnosed and treated in primary care without referral to hospital (11), with glucocorticoids (steroids) the mainstay of treatment (12, 13). Response to steroids is considered a key feature of PMR with it being a core criteria in several classification sets (14-16). This can lead to later unmasking of diagnoses once steroids are withdrawn, or alternatively, diagnoses may subsequently develop or evolve, for example, PMR transitioning to inflammatory polyarthritis (17).

Morbidity is not restricted exclusively to PMR, with GCA a medical emergency as due to ischaemia of the eye resulting in permanent visual loss in up to 35% of patients (18, 19). Visual loss and deterioration can be prevented by rapid initiation of high dose steroids (20). Steroid treatment regimens are not standardised in either condition and no steroid-sparing agents have been found to be effective as yet (21), although the results of the GiACTA trial (trial of tocilizumab in patients with GCA) are awaited at the time of writing this thesis. Prolonged

courses of glucocorticoid treatment are often undertaken, possibly because of clinicians' overriding concern to prevent blindness, increasing the risk of toxicity including cataract and glaucoma and other well-documented problems. In the UK, 62% of patients with PMR/GCA are prescribed steroids long-term with a median duration in excess of 1.2 years, with a one to three interquartile range of between 0.6 and 2.5 years (22). This trend has been increasing and due to the changing demographic of the UK population towards an older median age, more people are likely to be diagnosed with PMR and GCA, making reversal of this trend unlikely.

During 1990 – 2001, PMR incidence in the UK was estimated to be 84 per 100,000 person years (23), although comprised community treated patients, this study failed to apply classification criteria making comparison to other studies difficult.

Giant Cell Arteritis (GCA), is the commonest systemic vasculitis in the western world (24), although the incidence of GCA varies across countries: the highest rates are reported in Nordic countries, the UK and the US (23, 25-27). Its incidence estimate in the UK from 1990 - 2001 was 22 per 100,000 person years (23), but again without applying the current classification set for the disease. The incidence of PMR, taken together with GCA in patients aged >60yrs, is higher than that of rheumatoid arthritis, a difference increasing to more than tenfold in people aged >70yrs. Due to the problems of either population selection

or inability to apply classification criteria, data on the occurrence of disease outcomes is difficult to interpret particularly if studies have included different methods of case selection and definition. This extends to ocular complications in GCA, where recruitment of exclusively treated hospital patients leads to wide variation in the reported risk of blindness (with further detail given in 2.3.1).

1.1.1 Ocular complications

Approximately one in twelve patients with GCA will suffer monocular blindness. From hospital case series analysis, the commonest ocular complication is anterior ischemic optic neuropathy (AION). Other ocular ischaemic changes include central arterial or branch retinal arterial occlusion (CRAO or BRAO), choroidal ischaemia and posterior optic neuropathy (PION) (28). A prospective case series of 170 patients from the USA with biopsy-proven GCA showed 69 had AION (40%), 12 had CRAO (7%) and six had PION (3%). Fluorescein angiography was carried out in 55 of these 170 patients with 12 having detectable cilioretinal artery occlusion (21%). Nearly all patients had evidence of posterior ciliary artery occlusion on fluorescein angiography (28). In another retrospective study of 47 patients from Switzerland with GCA who had undergone fluorescein angiography, 22 had AION (47%), 17 had choroidal ischaemia (36%) and 7 had CRAO (15%) (29).

Magnetic Resonance Imaging (MRI) is helping to document further ischaemic changes affecting the ocular circulation. A study using high

resolution MR imaging of 43 patients with GCA demonstrated that 20 (46%) patients had mural enhancement of the ophthalmic artery suggesting inflammation (30).

Despite the significance of these diseases to patients and practising physicians in primary and secondary care, current data about risk factors are inconsistent and limited through retrospective study design or small sample size. The aetiology of PMR and GCA has hitherto been studied using case-control designs with the inherent risks of recall bias and finding representative control groups. As a result the epidemiology of PMR and GCA and risk factors for disease onset and progression need revisiting. In particular, patients with these conditions need to be recruited from community-based populations, but importantly, current classification sets need to be applied in order that results can be comparable to other future studies.

The development of large cohort studies now affords the opportunity to study in detail the descriptive epidemiology of both PMR and GCA and examine risk factors for disease development and progression. Prospective cohorts are of great value since information on risk factors is collected prior to disease onset negating problems of recall bias and since disease status is unknown at the start of observation, controls should be representative to subsequent cases.

The aim of this thesis is to describe the epidemiology of both conditions from community-based cohorts and a large international collaborative

study using longitudinal time-to-event analysis to investigate both factors associated with disease development and progression, with a particular focus on eye disease.

CHAPTER 2 BACKGROUND

2.0 SUMMARY

This chapter describes the clinicopathological features of PMR and GCA, their treatment, the arterial blood supply to the eye; to summarise the epidemiology of PMR and GCA and the published risk estimates for eye morbidity associated with GCA. A discussion with a particular emphasis on the risk factors for disease development and progression is presented. The differences between diagnosis and classification criteria is discussed. The major themes to be addressed in this thesis are outlined, namely: the need to provide community-based estimates of incidence and prevalence that are able to apply classification criteria; to study aetiological factors in prospective cohort studies; and to describe retinal changes and ocular outcomes from large adequately powered studies. A description of the datasets to be used and their value in being able to address these aims is presented.

2.1.0 Clinicopathological features of PMR and GCA

This section outlines the main the clinical and pathologic features of PMR and GCA, the tests used in current practice to establish their diagnosis, and the common pharmacological approaches to treatment.

2.1.1 Clinical features of PMR

Barber first used the term Polymyalgia rheumatica (PMR) in 1957, to describe a sudden onset inflammatory condition typified by stiffness and pain of the shoulder and pelvic girdles associated with constitutional effects (31). The condition previously carried numerous other names, with Bruce in 1888 describing cases of senile rheumatic gout (1). In this paper he notes "There is, perhaps, no disease as to which professional opinion differs more than as to rheumatic gout. This diversity of views is unfortunate, as it affects the kind of treatment and mode of life of the patient, and it disturbs the lay mind and gives occasion for remarks as to the uncertainties of medicine."

This uncertainty continues to the current day as in common with many rheumatic diseases, they are defined by common patterns of symptoms and physical signs. There are no specific diagnostic tests for PMR, a clinical diagnosis is made based on history, examination findings, often raised inflammatory markers and exclusion of other diagnoses. Typically, onset of disease is rapid, within a fortnight, with pain and stiffness affecting the shoulder and hip girdles, which may be accompanied by

general malaise, peripheral joint synovitis, weight loss and depression. Patients with PMR often have raised C-reactive protein (CRP) and or erythrocyte sedimentation rate (ESR). As a result, there is some uncertainty as to whether all cases classified as having PMR in studies actually have PMR or another diagnosis and may result in patients being treated with long-term steroids unnecessarily (32-34). The most recent classification set highlights the importance of excluding alternative diagnoses when making a diagnosis of PMR (35). Further discussion on the difference between diagnosis and classification is given below in Section 2.2.0. In the research setting, use of ultrasound, ^{18F}-FDG-PET and MR imaging are providing further evidence of additional clinical features (36-38). Due to increased cost, workforce planning and agreed standards for diagnostic validation, currently these imaging modalities have limited and variable clinical utility in routine everyday practice.

2.1.2 Treatment of PMR

The usual rapid response to treatment with glucocorticoids has been used in classification sets for the disease (14, 16, 39). Prior to the 1960s, treatment with glucocorticoids was reserved for more severe cases, with salicylates suggested as the first line agent (40). Since then glucocorticoids have become the standard treatment for polymyalgia rheumatica (41, 42).

As with many conditions, no ideal glucocorticoid regimen has been formally tested using a placebo controlled, double-blind randomised trial.

Despite this, national guidance suggests an initial starting dose of between 12.5 mg to 25 mg daily of prednisolone, continued for two to four weeks, with an aim of reaching 10 mg once daily after four to eight weeks (43, 44). Once the dose of 10 mg once daily is reached, a reduction by one mg per month is generally recommended (43). This slow withdrawal phase was perhaps first suggested by Hart in 1969 (45), and is supported by more recent observational data (46), and in a systematic review (47). The national guidance regimens would seem to suggest the earliest steroids can be stopped would be 44 to 50 weeks after commencing prednisolone (43, 44).

However, many patients with PMR are unable to stop their steroids within this time-frame: observational data from the US from the 1980s showed 40% of patients with PMR were only able to stop their glucocorticoids in a mean time of 95 weeks, with 40% estimated to have a glucocorticoid regimen of longer than four years (48). UK data similarly reveals a year-on-year trend for increasing median duration of steroid therapy: data from the Health Improvement Network (THIN) for UK adult patients registered with contributing general practices between January 1989 and December 2008 (22) show that in 1991 the median duration of steroid therapy for men with PMR/GCA was men was 53 weeks (CI 95% 28.4, 126.1) and 58 weeks (CI 95% 28.4, 122.9) for women; by 2005 it had reached 56.7 weeks in men (CI 95% 33.6, 101) and 63.7 weeks (CI 95% 32.3, 128.3) in women (22).

These data seem to demonstrate a reluctance to discontinue steroids in patients with PMR. This is of particular concern in view of the increasing awareness of the risks associated with long-term steroid use even at what might previously have been regarded as safe 'physiological' doses.

Well-recognised adverse effects of cumulative steroid exposure include: eye related morbidity (cataracts, glaucoma), cardiovascular risk factors (hypertension, diabetes), increased risk for infections and fragility fractures (49). A Task Force endorsed by the European League Against Rheumatism (EULAR) produced recommendations for steroid therapy in rheumatic diseases. Following a systematic review of 18 studies, the following adverse event rate per 100 patient years of follow-up was reported: eye morbidity (cataracts, glaucoma) 4/100, cardiovascular morbidity (dyslipidaemia, oedema and electrolyte imbalance, renal and heart dysfunction, hypertension) 15/100, endocrine morbidity (glucose intolerance and diabetes, fat redistribution, hormone dysregulation) 7/100, infections (viral, bacterial, skin) 15/100 and musculoskeletal morbidity (osteoporosis, osteonecrosis, myopathy) 4/100 (49).

2.1.3 Clinical features of GCA

The first description in the medical literature of a case thought to be due to GCA is by Hutchinson in 1890 (50). He described an elderly man with red streaks on his head who was unable to wear a hat due to pain. These streaks extended from the temporal region to almost the middle of the scalp, with several branches of each artery unable to be traced. The

pulses in the affected vessels were feeble initially, but after a week they were left as impervious cords. It was not until 1932 that the characteristic histological appearance of giant cells was described and only in 1938 that blindness was recognised as complication of the disease (51, 52).

Although temporal artery biopsy is often considered the gold standard, even today, a diagnosis is made typically on clinical grounds in a patient older than 50 years of age developing a new onset headache (although headache is not a prerequisite for the condition) in association with elevation of the erythrocyte sedimentation rate and/or CRP (53). Other clinical features include myalgia and stiffness (suggestive of co-existing PMR), visual disturbance, weight loss, jaw claudication, low grade fever, fatigue and depression (54, 55). Haematological and biochemical analysis often reveals raised inflammatory markers, with or without thrombocytosis, and sometimes anaemia (56).

Temporal artery biopsy, demonstrating granulomatous inflammation with or without giant cells, may confirm the diagnosis but this investigation is not carried out in all cases and because the pathological changes are not continuous, meaning the inflamed part of the artery is not captured within the specimen, may give a false negative result (57). Untreated GCA can lead to blindness and can occur prior to prompt treatment in up to 20% of cases, despite the use of steroids (58).

As in PMR, newer imaging modalities are proving useful in the diagnostic approach to GCA. The use of ultrasound, ^{18F}-FGD-PET, CT angiography and MRI reveal distinctive clinical features and help to display the extent and distribution of the vascular lesions in the disease (59). A multi-centre study evaluating the use of ultrasound to temporal artery biopsy concluded that ultrasound was more sensitive but less specific than biopsy in the diagnosis of GCA (60). Results from a meta-analysis of ^{18F}-FGD-PET revealed a pooled sensitivity of 83.3% and specificity of 89.6% for a diagnosis of GCA (61). Although, these expensive tests are not used in diagnosing every case in routine practice they do at least reveal the distribution of vascular involvement possible in GCA.

2.1.4 Anatomical distribution of vascular involvement in GCA

Giant cell arteritis is considered a large vessel vasculitis as it predominantly affects the aorta and its major branches (62). Other commonly affected arteries are the carotids, subclavian and axillary arteries and aorta (63). Several historical autopsy studies and case series have described the arterial burden of GCA, with aortic involvement described most commonly (64-66).

Aortic aneurysm or dissection is a relatively common complication of GCA thought to occur in 18 patients per 1000 person years at risk (67, 68). The increasing use of ^{18F}-FGD-PET combined with computer tomography

(^{18F}-FGD-PET CT) is revealing the extra-cranial extent of large vessel involvement. In a French case series, positive ^{18F}-FGD-PET CT findings were demonstrated in 69/130 patients with GCA with the 78% of patients having thoracic aorta involvement, 72% with subclavian involvement and 55% with abdominal aorta involvement (69). Positive ^{18F}-FGD-PET CT findings at diagnosis were correlated with subsequent aortic complications during follow-up (all nine cases of aortic complication had a positive ^{18F}-FGD-PET CT at baseline) (69).

Arterial patterns of involvement appear to be different for GCA compared to the closely related large vessel vasculitis, Takayasu's arteritis. In a study of arteriographic lesions between 145 patients with Takayasu's and 62 patients with GCA, cluster analysis revealed a symmetrical pattern of involvement and disease of subclavian and axillary arteries more commonly in patients with GCA than Takayasu's (70).

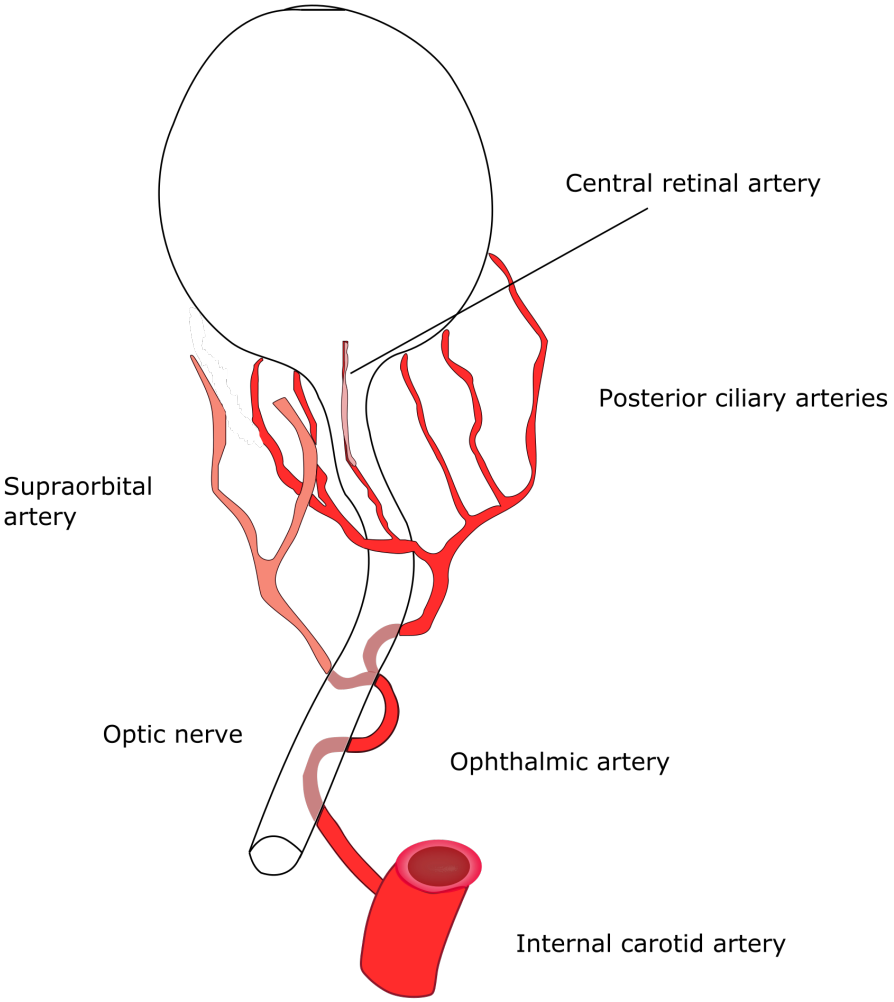
Case series describe vasculitic lesions typical of GCA affecting the aorta, its major branches and more distal branches in the head and neck, including the arterial supply to the eye (69). Perhaps the most feared complication associated with GCA is blindness associated with ischaemia of the medium and small vessels which form the arterial supply to the eye. GCA is known classically to involve the superficial temporal artery which is around 2 mm in outside diameter in keeping with the size of a medium vessel (71). The ophthalmic artery is smaller still, with a diameter of 1.54 mm in males and 1.31 mm in females from one

anatomical series of 71 Caucasian patients (72). Branching from the ophthalmic artery, the central retinal artery has a diameter of around 160 microns (73). In summary, it would be wrong to conclude that GCA is purely a large vessel vasculitis and the Chapel Hill Nomenclature makes note of this (62).

2.1.5 Arterial supply to the eye

The blood supply to the eye is particularly at risk in GCA. The arterial supply of the globe arises from branches of the ophthalmic artery, which branches from the internal carotid artery once the latter has entered the skull through the carotid canal. There is considerable variation in the course and subsequent branching pattern from the ophthalmic artery (74, 75). However, generally on exiting the skull vault through the optic canal, the branches of the central retinal artery and posterior ciliary arteries arise from the ophthalmic artery (74-76) See Figure 2.1. Both the central retinal artery and the posterior ciliary arteries can supply the nutritive collaterals to the optic nerve, with only the central retinal artery then entering the optic nerve (intraneural course), prior to dividing further close to the surface of the optic disc to form the central retinal branches (usually two superior and two inferior vessels) (74-76). The posterior ciliary arteries, usually two or three (as many as five), run forward, pierce the sclera and supply the choroidal vessels and are responsible for 70 to 80% of blood flow to the retina (74, 76, 77).

Figure 2.1 eye vasculature



2.1.6 Arterial distribution in relation to blindness

The commonest ocular complication from hospital case series analysis is anterior ischemic optic neuropathy (AION), although central arterial or branch retinal occlusion (CRAO), choroidal ischaemia and posterior optic neuropathy (PION) have all been reported (28). Previous autopsy series have revealed that the ophthalmic artery is most commonly affected by

GCA. Case series from the 1940s describe 18 cases with post-mortem findings describing involvement of the ophthalmic artery and its branches (see Table 2.1). Of the case reports with histological assessment of the eyes, only three cases from the 18 described reveal inflammatory changes affecting the retinal branches on the fundus. The reasons for this apparent tropism are unknown.

Table 2.1 Histopathologic features of eye vascular involvement from autopsy series

Author	Study type	Extent of arterial involvement	Histopathologic changes
Cooke et al 1946 (66)	Description of seven case, two of which underwent post-mortem examination, with only one examining the vessels to the eye	Both eyes, retinal arteries and its branches	Infiltration with inflammatory cells with giant cells affecting the adventitia and media. Fragmentation and calcification of the internal elastic lamina.
Cardell and Hanley 1951 (78)	One case – post mortem examination	Left eye, ophthalmic and right eye posterior ciliary arteries	Typical changes of giant cell arteritis with inflammatory cell infiltrate together with periadventitial giant cells around the left ophthalmic artery.
Kreibig 1953 (79)	One case – post mortem examination	Ophthalmic artery and vessels of the circle of Zinn	Severe pan-arteritis with granulomatous formation and proliferation of the intima.
Heptinstall et al 1954 (80)	Case series of 14 cases two with post mortem examinations.	One case (case 14) had involvement of right and left ophthalmic arteries	Inflammatory cell infiltrate with fragmentation of the internal elastic lamina.
Crompton 1959 (81)	One case – post mortem examination	Both eyes were examined. Left eye: ophthalmic, posterior ciliary, circle of Zinn, central retinal artery and branches over the disc rim. Right eye: similar to left including a nasal branch of central retinal artery.	Lymphocytic infiltrate with presence of giant cells.
Spencer and Hoyt 1960 (82)	One case – post mortem examination	Both eyes were examined with involvement of the ophthalmic and posterior ciliary arteries.	Chronic inflammatory infiltrate affecting the media. Intimal thickening and giant cells with granulomatous necrosis was also noted.

Author	Study type	Extent of arterial involvement	Histopathologic changes
Cullen 1963 (83)	Five cases reports of which one case had a post mortem examination	Both eyes were examined revealing involvement of the ophthalmic, posterior ciliary and central retinal artery at its origin.	Typical lesions of giant cell arteritis.
Manschot 1965 (84)	One case – post mortem examination	Right eye – central retinal artery intradural course and one posterior ciliary artery	Loss of internal elastic lamina, reduplication of the intima and thrombus formation in the lumen leading to central retinal artery occlusion.
Wolter and Phillips 1965 (85)	One case – histopathologic assessment of the right eye following enucleation due to haemorrhagic glaucoma.	Right eye – ophthalmic and posterior ciliary arteries	Inflammatory cell infiltrate, giant cell and thickening and fractures of the internal elastic lamina.
MacFaul 1967 (86)	One case – post mortem examination	Right eye – short ciliary arteries Left eye – ciliary arteries around the optic nerve	Right eye – short ciliary arteries showed intense inflammatory cell infiltrate with giant cells Left eye – giant cells
Wilkinson and Russell 1972 (87)	Four cases – post mortem series	Three out of four had ophthalmic artery involvement, two with central retinal involvement and two with posterior ciliary artery involvement.	Typical changes of giant cell arteritis
Butt, Cullen and Mutlukan 1991 (88)	Three cases – two of which underwent post-mortem examination	Case one – both eyes – ophthalmic and posterior ciliary vessels. Case two – right eye – ophthalmic artery but not central retinal artery	Inflammatory cell infiltrate principally in the media with destruction of the internal elastic lamina and intimal thickening.

2.1.7 Treatment of GCA

High dose glucocorticoids (GCs) are the mainstay of treatment, with evidence of benefit demonstrated since the 1950s (89, 90). However, there is no consensus on the optimal treatment for GCA, and there is considerable variation in clinical practice with regard to the initial (starting) dose, and subsequent rate of dose-reduction of GCs (91). Both the European League Against Rheumatism (EULAR) and British Society for Rheumatology (BSR) and have produced guidelines on GCs dosing. The guidelines were developed through extensive literature search using a modified Delphi technique. Recommendations were based on data from clinical trials and expert opinion of the panel members (92, 93). The EULAR guideline advises treatment with prednisolone 1 mg/kg/day (maximum 60 mg/day) continued for 1 month before entering a tapering phase over several months (92). The BSR recommends prednisolone 40 to 60mg (not <0.75 mg/kg) daily until the resolution of symptoms and laboratory abnormalities in patients without visual loss; 500mg to 1g of intra-venous methylprednisolone in those with evolving visual loss; and at least 60mg a day for those patients with established visual loss before then entering a tapering phase (93). The BSR guidelines and currently being revised and are due to be published in 2017.

Steroid sparing agents have been trialled in the treatment of GCA with formal randomised studies of IV-methylprednisolone, methotrexate, dapsone, hydroxycholoroquine, and two anti-TNF agents (infliximab and

adalimumab). The results have not shown a benefit for the use of adjunct agents at the time of diagnosis but methotrexate may have a marginal benefit for subsequent relapse (94, 95). A randomised trial of the IL-6 blocker tocilizumab in the treatment of GCA (GiACTA) is due to report in due course (96) but the preliminary results presented at the American College of Rheumatology look promising. Lack of positive results from the clinical trials, may in part, be due to methods of case selection and definitions of disease.

2.2.0 CLASSIFICATION AND DIAGNOSTIC CRITERIA

Whilst there are many classification sets, no criteria have been fully validated for clinical diagnosis of PMR and GCA. Rather, a diagnosis is made, based on typical patterns of disease and usually rapid response to steroids. Those case which are then diagnosed with the condition can then be scrutinised by classification criteria to produce a sample of patients which should be representative to other studies who have used similar methods of case ascertainment, selection and definition. If these methods differ between studies, then comparison of factors for both disease onset and progression can be difficult to interpret.

2.2.1 Classification criteria for PMR and GCA

Both conditions are difficult to define not least due to the lack of a single sensitive and specific diagnostic test. In addition there are different classification criteria sets in existence used to define the two conditions,

and particularly for PMR, helping to contribute differences in the way the studies were designed and the ultimately the estimates derived (see Table 2.2).

Table 2.2 Classification Criteria for Polymyalgia Rheumatica

Authors & Year	Proposed Criteria	Requirement for Classification
Bird et al. (1979) (97)	Age ≥65 years Bilateral shoulder pain and stiffness; acute or subacute onset (<2 wk); morning stiffness >1 hr depression and/or weight loss; bilateral tenderness in upper arm muscles ESR >40 mm/hr	Any three, or any one plus temporal artery abnormality (including decreased pulsation, tenderness, beading or bruit).
Jones and Hazleman (1981) (14)	Shoulder and pelvic girdle pain; morning stiffness >1 hr; exclusion of rheumatoid arthritis or other inflammatory arthropathy, myopathy, malignancy ESR >30 mm/hr or CRP >6 mg/L Rapid response to corticosteroids	All criteria must be met
Chuang et al. (1982) (98)	Age ≥50 years >1 month bilateral aching and stiffness of at least two of the following areas: Neck or torso, shoulders or proximal arms, hips or proximal thighs; exclusion of other causes ESR >40 mm/hr	All criteria must be met
Healey and Wilske (1984) (15)	Age ≥ 50 years >1 month of neck, shoulder, or pelvic girdle pain (any two areas); morning stiffness >1 hr; exclusion of other diagnoses ESR ≥40 mm/hr Rapid response to daily, low-dose steroid therapy (i.e. prednisolone ≤20 mg)	All criteria must be met
Doran et al. (2002) (16)	Age ≥ 50 years; Bilateral aching and morning stiffness (lasting ≥ 30 min) persisting for at least 1 month and involving 2 of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs ESR > 40 mm/hr OR rapid response to corticosteroids	All criteria must be met
Dasgupta et al. (2012) (99)	EULAR/ACR criteria: Morning stiffness ≥ 45 minutes (2 points); Hip pain, limited range of movement (1 point) Absence of other joint pain (1 point) Negative RhF or ACPA (2 points) Ultrasound criteria: at least 1 shoulder with sub-deltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis AND at least 1 hip with synovitis and/or trochanteric bursitis (1 point); both shoulders with subdeltoid bursitis, bicep tenosynovitis or glenohumeral synovitis (1 point)	All patients must be: Age ≥50 years, have bilateral shoulder aching and abnormal ESR/CRP Scoring algorithm without ultrasound score of 4 needed – with ultrasound score of 5 needed

The current classification criteria for GCA were published in 1990 by the American College of Rheumatology (ACR) (100). They comprise the following features:

1. Age at disease onset >=50 years,
2. New headache,
3. Temporal artery abnormality (tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries),
4. Elevated ESR (>=50 mm/hour by the Westergren method),
5. Abnormal artery biopsy (showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells) (100).

For purposes of classification, a patient shall be said to have giant cell arteritis if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%.

Any objective enquiry into the epidemiology of PMR and GCA requires a consistent approach to case definition. This is difficult for diseases which are almost entirely recognised based on their clinical features. Although diagnostic tests are available they lack specificity and the gold standard for GCA (temporal artery biopsy) lacks sensitivity. The classification criteria sets reflect commonly acknowledged aspects of disease, although differences in their criteria are likely to result in variation of measures of disease occurrence.

2.3.0 PREVALENCE OF PMR AND GCA

Prevalence and incidence estimates for PMR and GCA vary widely. This may, in part, represent true geographic or genetic differences in the populations studied (see Table 2.3). Only one study on the community prevalence of GCA and PMR in the UK has been conducted by Kyle *et al* from a single Cambridgeshire practice in 1985 and has not been repeated since (101). The prevalence estimate of GCA was 1.23% for those aged ≥65 years (101) and for GCA combined with PMR was 3.5% (101). However, that study pre-dates the current ACR classification criteria set and failed to include participants younger than 65 years. More recent data from Europe and the USA have given an over 30-fold discrepancy in prevalence estimates, (see Table 2.3). Data from the Mayo clinic from all incident cases of GCA from Olmsted County (years 1950 to 1999) revealed 173 cases of GCA in those aged ≥50 years. This resulted in a prevalence estimate for GCA of 0.23% and for PMR of 0.74% (95% CI 0.67 to 0.81) (16, 102, 103). An invited questionnaire population survey of household residents in Portugal gave a prevalence estimate of 0.1% (95% CI 0.0 to 0.2) for PMR: however since 41.5% of those surveyed were aged 50 years, restricting this to those aged older than 50 years would result in a higher prevalence estimate (104). In 2006, questionnaires sent to hospital departments and insurance companies in Germany revealed a prevalence for GCA of 0.04% (95% CI 0.04 to 0.05) (105).

Table 2.3 Published estimates for PMR and GCA prevalence

Author	Country; survey type; age threshold	PMR and GCA prevalence	Classification
Branco et al 2016 (104)	Portugal; Survey of one adult per household with questionnaire and possible review by clinician >18 years.	PMR: 0.1% (0.0% to 0.2%)	PMR Bird et al
Romero-Gomez et al 2015 (106)	Spain; Single hospital in Marbella 2010 point prevalence; ≥50 years	GCA 0.01% (95% CI 0.006 to 0.02)	GCA: ACR 1990
Herlyn et al 2014 (105)	Germany; Survey of hospitals, private physicians and insurance companies in 2006; ≥50 years	GCA: 0.04% (95% CI 0.04 to 0.05)	GCA: ACR 1990
Mohammad et al. 2011 (107)	Sweden; survey of Skåne cumulative incidence 1997 – 2010; ≥50 years	GCA: 0.11% (95% CI, 0.10-0.12).	GCA: Temporal artery biopsy positive only
Bernatsky et al 2009 (108)	Canada; hospital record survey, cumulative incidence 1995 -2006; ≥50 years	PMR: 0.64% (urban); 0.86% (rural)	PMR: Physician billing twice within 2 months or stated on hospital discharge.
Pamuk et al 2009 (109)	Turkey. Single rheumatology department in a tertiary referral centre, cumulative incidence, ≥50 years	PMR and GCA: 0.02%	PMR: Chuang et al GCA: ACR 1990
Lawrence et al 2008 (102) Salvarni et al, 1999 (103). Doran et al 2002 (16).	USA; Olmsted County survey of cumulative incidence 1950 -1999; ≥50 years	PMR: 0.74% (95% CI, 0.67–0.81) GCA: 0.28% (95% CI, 0.19–0.27) -	PMR: Doran et al GCA: ACR 1990
Salaffi et al 2005 (110)	Italian MAPPING study; population survey; age ≥65 years	PMR: 0.37% (95% CI 0.29-0.44)	PMR: Bird et al
Koboyashi et al 2003 (111)	Japan; Hospital only treated patients in 1997; ≥50 years	GCA: 0.002%	GCA: ACR 1990
Kyle et al 1985 (112)	UK; GP practice based survey; ≥ 65 years.	PMR: 1.69% (95% CI 0.70 to 2.68) GCA: 1.23% (95% CI 0.38 to 2.08)	PMR: Jones and Hazleman GCA: Jones and Hazleman

2.3.1 Incidence of PMR and GCA

Published incidence estimates for PMR and GCA are shown in Table 2.4, with incidence for both conditions increasing with age. Data from the Mayo clinic gave an incidence for PMR of 55.6 per 100,000 population aged over 50 years for men and 72.7 for women. The greatest annual incidence was seen in persons aged 70 to 79 years: 124.3, 181.7 and 155.7 per 100,000 person years for men, women and overall, respectively (113). An Italian study from a large single hospital, serving a population of around 500,000 people, reviewed temporal artery biopsies to ascertain the incidence of GCA. The annual incidence for those aged older than 50 was 5.8 per 100,000 person years. The highest incidence was seen in people aged between 80 and 84 years, 16.7 per 100,000 person years (95% 12.9, 21.4) (114).

The wide variation in the estimates (see Table 2.4) may arise since earlier studies refer to patients with temporal arteritis or polymyalgia rheumatica as having the condition GCA, using the later as an umbrella term to encompass both conditions, leading to confusion and difficulty in making comparison to more contemporary studies (115, 116). The estimates from the Mediterranean countries are around a factor of ten lower than those from the Scandinavian countries, the UK and USA, and these differences cannot be explained through differences in study design alone.

Table 2.4 Published estimates for PMR and GCA incidence

Author	Country; survey type; age threshold	PMR and GCA incidence per 100,000	Classification
Raheel et al 2016 (113) Chandran et al 2015 (117) Salvarani et al 2004 (118) Chuang et al 1982 (98)	USA; Olmsted County survey of annual incidence; PMR 1970-1979 and 2000-2014; ≥50 years GCA; 1950-1999 and 2000 – 2009; ≥50 years	PMR: 63.9 (95% CI 57.4 to 70.4) and 53.7 (43.5 to 65.6) GCA 18.8 (95%CI 15.9 to 21.6) and 19.8 (95% CI 15.2 to 24.3)	PMR: EULAR/ACR and Chuang et al GCA: ACR 1990
Catanos et al 2016 (114)	Italy, histopathology review from single hospital in Reggio Emilia province, annual incidence 1986-2012, ≥50 years	GCA: 5.8 (95% CI 5.1 to 6.5) -	GCA: Temporal artery biopsy positive only* (91% fulfilled ACR 1990)
Elfving et al 2016 (119)	Finland; Hospital treated patients with GCA from five hospitals serving Northern Savo annual incidence 2010; ≥50 years	GCA: 7.4 (95% CI 6.3 to 8.7)	GCA: ACR 1990
Romero-Gomez et al 2015 (106)	Spain; Single hospital in Marbella GCA annual incidence 1994-2010; ≥50 years	GCA 2.2 (95% CI 1.4 to 3.0)	GCA: ACR 1990
Smeeth et al 2006 (120) Petri et al 2015 (121)	UK; GP research database, annual incidence, PMR 1990-2001; ≥50 years GCA 2010-2011; ≥50 years and GCA 1990 to 2001; ≥50 years.	PMR 84.2 (95% CI 83.0 to 86.0) GCA 22.0 (95% CI 21.0 to 23.0) and GCA 11.2 (95% CI 10.9 to 11.5)	1 record of either GCA or PMR and at least 2 prescriptions for glucocorticoids (Smeeth) and GCA: > 1 record for GCA and >1 prescription for systemic glucocorticoid (Petri)
Mohammad et al 2015 (122)	Sweden; histopathology review of four health centres in county of Skåne annual incidence GCA; 1997-2010; ≥50 years	GCA: 14.1 (95% CI 13.1 to 15.0)	GCA: Temporal artery biopsy positive only*

Author	Country; survey type; age threshold	PMR and GCA incidence per 100,000	Classification
Dunstan et al 2014 (123)	Australia; histopathology review from three health centres in South Australia; annual incidence GCA 1992-2011; ≥50 years	GCA: 3.2 (95% CI 2.8 to 3.6)	GCA: Temporal artery biopsy positive (all fulfilled ACR 1990)
Bas-Lando et al 2007 (124)	Israel; hospital record review from four hospitals in Jerusalem, annual incidence GCA 1980 -2004; ≥50 years	GCA: 11.3 (95% CI 9.5 to 13.1)	GCA: temporal artery biopsy positive** or if diagnosed with GCA and met ACR 1990.
Gonzalez-Gay et al 2007 (125) Gonzalez-Gay et al 2001 (126)	Spain; single hospital record review in Lugo, annual incidence for GCA 1981-1988 and 1981-2005, ≥50 years	GCA 10.2 and 10.1	GCA: temporal artery biopsy positive
Haugeberg et al 2000 (127)	Norway; hospital record review from Vest Agder County, annual incidence GCA 1992-1996; ≥50 years	GCA: 32.8 ()	GCA: ACR 1990 (94% temporal artery biopsy positive)
Gran and Myklebust 1997 (128)	Norway; clinical review of GP suspected cases annual incidence for GCA and PMR 1987-1994, ≥50 years	PMR 112.6 GCA 29.0	PMR: Bird et al GCA: temporal artery biopsy positive only
Elling et al 1996 (129)	Denmark; national register review of hospital cases supplemented by histopathology department review in two hospitals annual incidence of PMR and GCA 1982-1994, ≥50 years	PMR 41.3 (95% CI 30 to 67) GCA 20.4 (95% CI 19 to 23)	PMR: Hospital recorded cases GCA: Hospital recorded cases, TAB positive rate 15% (for all TAB)
Baldursson et al 1994 (130)	Iceland; national register review supplemented with histopathology review of temporal artery biopsies, annual incidence of GCA 1984-1990, ≥50 years	GCA: 27.0 (95% CI 22.7 to 32.1)	GCA: ACR 1990 (65% of temporal artery biopsies had giant cells present)
Franzen et al 1992	Finland annual incidence of GCA 1984-1988, ≥50 years	GCA: 22.7	GCA: temporal artery biopsy positive

Author	Country; survey type; age threshold	PMR and GCA incidence per 100,000	Classification
Salvarani et al 1991 (131)	Italy; single hospital in Reggio Emilia province, annual incidence PMR and GCA; 1980-1988; ≥50 years	PMR 12.7 GCA 6.9	PMR: Chuang et al GCA: Temporal artery biopsy positive and Clinical features of GCA***
Boesen and Sorensen 1987 (116)	Denmark; postal survey of all general practitioners and hospital departments in the county of Ribe, annual incidence of GCA 1982-1985, ≥50 years	GCA 23.3 (temporal biopsy positive) Combined PMR with GCA: 76.6	GCA: Clinical criteria or biopsy positive****
Kyle et al 1985 (112)	UK; single GP practice based survey; annual incidence ≥ 65 years	PMR 211.5 GCA 153.8	PMR: Jones and Hazleman GCA: Jones and Hazleman
Bengtsson et al 1981 (115)	Sweden; hospital record review from two hospitals in the city of Göteborg, annual incidence of GCA and PMR 1973-1975, ≥50 years	GCA: 18.3 GCA and PMR combined: 28.6	GCA: Clinical criteria and temporal artery biopsy positive cases*****. PMR: Clinical criteria†
Jonasson et al 1979 (132)	UK; Lothian region of Scotland annual incidence of biopsy positive GCA 1964-1977	GCA: 4.23	GCA: positive temporal artery biopsy**
Cameron 1959 (133)	Single GP practices in Kent of 3,700 registered patients 21% > 60 years age	GCA: 165	GCA: clinical diagnosis of the nine cases described

Temporal artery biopsy defined studies used a single senior or experienced histopathologist to review specimen with only biopsies showing: inflammatory cell infiltrate or granulomatous inflammation with or without giant cells considered positive, except the following: *which included: segmental loss or disruption of the internal elastic lamina; compromise and/or obliteration of the arterial lumen; atrophy and scarring of the muscularis; and adventitial fibrosis as positive findings. **No definition of what constituted a positive biopsy are given. ***GCA required at least four of the following: abnormal temporal arteries (tender and swollen), loss of vision, jaw claudication, presence of PMR and response to glucocorticoids. ****temporal artery positive or clinical criteria: pain and stiffness in proximal muscle groups for at least 2 weeks without evidence of inflammatory arthritis or pain, tenderness or abnormal findings on palpation of the temporal artery. *****temporal artery positive definition: destruction of the internal elastic lamina and infiltration of mononuclear cells, clinical criteria (all needed to be met): pain and stiffness of proximal muscles without evidence of inflammatory arthritis, elevated ESR, no evidence of malignancy, RA, SLE or PAN, prompt and long-lasting response to glucocorticoids. †Clinical criteria for PMR: constitutional symptoms with proximal muscle pain and stiffness, raised ESR, no signs of inflammatory arthritis and no head symptoms.

2.3.2 Comments

The contemporary epidemiology data from the UK are old and inadequate, and there is need to apply classification criteria consistently if the results from studies are to be directly comparable.

2.4.0 ESTIMATES OF OCULAR MORBIDITY

Published information on the occurrence of eye disease in GCA has been based almost exclusively on small hospital-based patient series (134, 135). No accurate data exist on the prevalence and nature of eye complications among patients in the community and no comprehensive assessments undertaken of the full range of ocular morbidity in patients with GCA due to both the disease process, and treatment with glucocorticoids. To date the focus has been on the disease process itself, rather than any iatrogenic associated outcome from long-term exposure to glucocorticoids.

2.4.1 Ocular sequelae from GCA

Recently published data from the Mayo clinic revealed that 47 from 204 patients with GCA had visual symptoms prior to diagnosis of GCA. Of these, seven patients had monocular blindness and two had binocular blindness. AION was noted in 17 patients and CRAO in two patients as the cause of visual disturbance. This study data from residents from Rochester (Olmstead County, Minnesota USA) estimates that around

30,000 residents are aged >50yrs. Neither long-term data on eye disease nor the effect of steroids on eye morbidity are described (136).

From information on the occurrence of eye disease in GCA based almost exclusively on small hospital-based patient series (134, 135), the most common reported outcome is of visual loss, reported in a number of ways, including transient or permanent, monocular or binocular involvement. Permanent visual loss occurs in 12% to 32% of patients. (137, 138). Definitions of severity of visual loss are also equally muddled as visual loss is reported either as reduced visual acuity or as loss of visual field. In addition, the lack of control group for these studies prevents calculation of relative and absolute risk estimates for visual loss in patients with GCA. Risk for eye complications appears to differ in subsets of patients with GCA, with those with isolated aortitis proving a particular diagnostic challenge (139-141).

From hospital case series analysis, the most common ocular pathology (Table 2.5) is anterior ischemic optic neuropathy (AION), with central arterial or branch retinal occlusion (CRAO), choroidal ischaemia and posterior optic neuropathy (PION) also reported (28).

Table 2.5 Common ocular complication in GCA

Cause	Mechanism
AION	Ischaemia of the posterior ciliary arteries which supply the optic nerve head
CRAO	Central retinal artery occlusion
PION	Ischaemia of the optic nerve within its intra-orbital, intra-canalicular, or intracranial tract

A prospective case series of 170 patients with biopsy-proven GCA revealed 69 had AION (40%), 12 had CRAO (7%) and 6 had PION (3%); 55 had fluorescein angiography and 12 of these had cilioretinal artery occlusion (21%). Most patients who fluorescein angiography showed evidence of posterior ciliary artery occlusion (28). Another retrospective study of 47 patients with GCA who had fluorescein angiography, showed 22 had AION (47%), 17 had choroidal ischaemia (36%) and seven had CRAO (15%) (29).

Use of MRI has revealed further changes affecting the eye: a study using high resolution MR imaging of the ophthalmic artery in 43 patients with GCA demonstrated that 20 (46%) of patients had mural enhancement, suggesting inflammation. Eleven of the 43 patients had an MRI scan prior to treatment with glucocorticoids, but no correlation was demonstrated between treatment prior to the scan and mural enhancement. In the 20 patients with mural enhancement, ophthalmic examination involving fundoscopy revealed fundal changes in seven patients, including AION and CRAO. The MRI and ophthalmic examination were normal in fifteen patients. Nine patients had AION (20%) four CRAO (9%) and one PION (2%). MRI showed vessel inflammation in patients who had no symptoms of visual disturbance, whereas another eight participants were MRI negative but had typical changes of arteritis on ophthalmic examination. As suggested by the authors, differences in agreement between symptoms, ophthalmic examination and MRI may be due to the study's imaging protocol. Only inflammation of the ophthalmic artery was

detected and not the small posterior ciliary arteries. Both the utility and significance of MRI changes require further evaluation (30).

As patients with GCA may be managed exclusively in a primary care setting, without referral for either temporal artery biopsy or ophthalmic department examination, there are no accurate data on the incidence, prevalence and nature of eye complications among patients in the community, although sudden dramatic deterioration in vision should prompt the affected patient to seek urgent medical attention.

Moreover, there have been no comprehensive assessments of the full range of ocular morbidity in patients with GCA due to both the disease process and treatment with glucocorticoids. It is therefore difficult to appreciate the risk of visual loss in patients with GCA, particularly those based in the community setting. In addition the absolute and relative risks are unknown making public health planning difficult.

2.5.0 BIOLOGICAL MECHANISMS OF DISEASE ONSET

Th-17 and Th-1 lymphocytes have been implicated in the pathogenesis of both diseases (142). Various cytokines have shown to be key in the development and maintenance of the inflammatory reaction within the vessel wall of patients with GCA, including IL-12, interferon gamma, IL-6, IL-17 and IL-21 (18, 143, 144). The triggers for the immune response to initiate disease onset are unknown. The major theories for the underlying

disease mechanism in PMR and GCA centre on the concepts of immunosenescence and endothelial dysfunction.

2.5.1 Immunosenescence

Although the causes of PMR and GCA are unknown, the strong positive association to older age suggests a role for immunosenescence. Thymic involution occurs with advancing age, with loss of T-cell development and decreased emigration of naïve T cells (145).

Dendritic cells appear to be central to the maintenance of the inflammatory process and for granuloma formation (146-149). The activation of the dendritic cells, based in the adventitia of arteries, leads to activation of CD4 positive T cells to polarise into Th1 and Th17 cells, and recruitment of CD8 positive cytotoxic T-cells and Natural Killer cells (150). Activation of macrophages coalesce to develop into multinucleated giant cells, the presence of which lead to the descriptive name of GCA. In addition, there is downregulation of regulatory T cells and the activated T-cell population brings about production of IL-17, interferon gamma and growth factors leading to inflammatory cell maintenance and remodelling of the arterial wall, resulting in increased risk of aneurysmal formation and ischaemic complications (151, 152). Amongst GWAS studies in patients with GCA, the consistent identification of *HLA-DR1*04* supports the central role for antigen presenting cells such as dendritic cells (153).

Dendritic cells are found in healthy arterial tissue at the adventitial-media border (a similar site to calcification deposits), but remain in an inactivated state. Dendritic cells are not usually found in healthy veins, but have been identified in venous pathologies such as at the sites of varicosities and in stenosis of venous coronary artery bypass grafts (154, 155). It is possible that endothelial damage may partially explain the activation of dendritic cells within arterial vessel walls. In addition, recruited T-Cells and macrophages activate endothelial cells of the vasa vasorum to express high level of adhesion molecules such intercellular adhesion molecule -1 (ICAM1) and ICAM2, P- and E- Selectin and VCAM-1 causing further immune cell recruitment (156), moreover, concentrations of soluble ICAM1 correlate with disease activity (157).

2.5.2 Endothelial Damage

The experimental laboratory studies and epidemiological data implicate endothelial dysregulation as being important drivers for disease development, particularly for GCA but also PMR. Moreover the relatively confined vascular tropism of GCA strongly suggests a role for the microenvironment, rather than purely a cell-mediated driven immune response. Previous histopathological studies of temporal artery biopsies identified calcific deposits in the internal elastic membrane, which in some cases had a focal giant cell reaction towards them (158). These calcific deposits are also present in the temporal arteries of individuals not thought to have GCA, more common in women and positively

correlated with increasing age (159). Plausible risk factors for endothelial damage include smoking, alcohol and obesity and other typical traditional cardiovascular risk factors, including hypertension and diabetes (160). These factors have been associated with alterations in systemic inflammation and endothelial function. Chemicals produced during cigarette smoking have been shown to be pro-inflammatory in human and animal models to be pro-inflammatory (161, 162). Obesity is recognised as a risk factor for the metabolic syndrome, with studies showing increased inflammatory cytokines, such as serum IL-6 and TNF (163). Moderate alcohol consumption has been shown to be cardioprotective in terms of coronary heart disease and may be protective in terms of reducing endothelial damage (164). It is possible therefore that these biological mechanisms are important in both GCA and PMR pathogenesis. However without more definitive data on risks and outcomes, all these mechanisms remain speculative.

2.6.0 RISK FACTORS FOR DISEASE DEVELOPMENT – ONSET AND PROGRESSION

This section summarises the risk factors for disease onset, in terms of associations with PMR and or GCA and disease progression, namely for ocular morbidity in GCA and inflammatory polyarthritis after a diagnosis of PMR. The risk factors are divided into non-modifiable and modifiable factors.

2.6.1 Non-modifiable risk factors-Genetic Determinants

Both PMR and GCA are considered auto-immune diseases. The highest incidence figures (See Table 2.4) are from Scandinavian countries whose population with PMR and GCA are almost exclusively Caucasian (165). Genome-wide association studies (GWAS) have been published and have been consistent in identifying the major histocompatibility complex (MHC) class II molecule and protein tyrosine phosphatase, *non-receptor type 22* (PTPN22) gene loci as important genetic determinants of interest (166). Genetic studies of PMR and GCA have revealed an association between the human leukocyte antigen *(HLA)-DRB1*04* allele but results have not always been consistent, particularly for PMR from southern European populations (167-173). There does appear to be a different genetic profile between GCA and the other closely related large vessel vasculitis of Takayasu's arteritis. GCA associates to HLA Class II, whereas Takayasu's most strongly associates with HLA Class I, suggesting a difference in the underlying genetic risk profile (174). Outside of the HLA region both types of LVV showed an association between a polymorphism located nearby the IL12B gene (174). In addition, in patient with GCA, other GWAS Single Nucleotide Polymorphism (SNP) loci outside of the HLA region include those involved in the *plasminogen gene and collagen prolyl 4-hydroxylase 2 (P4HA2)* the expression of which is controlled by hypoxia-inducible factor 1 (HIF-1) (175), the latter of which is involved in vascular remodelling by smooth muscle cells.

2.6.2 Genetic studies of PMR

A study of 55 patients satisfying Bird's criteria for PMR from southern France revealed an association between *HLA-DRB1*01* but not *HLA-DRB1*04* (odds ratios and 95% CI: 2.6 (1.3, 5.2) and 1.4 (0.7, 2.8) respectively) (172). In contrast, a study of 46 patients with PMR from the USA revealed a positive association with *HLA-DRB1*04* but was negatively associated with *HLA-DRB1*01* (percentage frequencies between cases and controls, 67.4% vs 23.6% and 10.9% vs 27.8% respectively) (169).

A SNP of the endothelial nitric oxide synthase gene (NOS3) known as *T-786C* predisposes to cardiovascular disease by reduced expression of nitric oxide synthase in response to sheer stress. This variant has been shown to be positively associated with PMR with an odds ratio of 2.48 supporting a role of endothelial dysregulation in patients with PMR (176).

2.6.3 Genetic studies of GCA

A UK GWAS study of 225 patients with GCA and 1378 controls revealed an association between *HLA-DRB1*04* carriage and GCA (odds ratio 2.69, 95%CI 2.02 to 3.58) (153). A meta-analysis of 14 previous published studies revealed an odds ratio of 2.45 for *HLA-DRB1*04* and GCA (153). In addition, familial aggregation has been reported for GCA with a literature review concluding, from published cases reports, the prevalence for familial GCA to be 1 in 83 (compared 1 to 250-500

expected by chance only) (177) with 18 of the 32 patients genetically screened carrying the HLA-DR4 antigen.

The adventitia of arteries affected by GCA is an important area involved in immunogenicity and is the only region of the vessel wall that is vascularised by the vasa vasorum (178). Dendritic cells are found within the arterial wall, particularly at the adventitia-media border (147). MHC class II is typically found on professional antigen presenting cells, such as dendritic cells which are responsible for naïve T-cell differentiation and development (179).

2.6.4 Other non-modifiable risk factors for onset

- Increasing age is a risk factor: these diseases are rarely diagnosed in those younger than 50yrs old, with this age cut-off forming one of the principal criteria for classifying both PMR and GCA. With incidence increasing with age, this association suggests that cumulative endothelial damage, immunosenescence and inflammation may be important in the development of both diseases in susceptible individuals.
- Sex: both conditions are commoner in women (107, 180, 181).
- Seasonal variation appears to influence diagnostic rates in some countries and although not confirmed, infective agents have been suggested as causal factors but not confirmed (182-184). Moreover data from the THIN database, infection *per se*, rather than individual microbes is associated with subsequent increased

incidence of GCA, with an apparent dose affect. The incidence rate ratio was 2.18 with more than five infections in the past (185). However, it is unknown whether infections cause GCA or whether those who have a lot of infections have a dysregulated immune system that puts them at both increased risk of infection and GCA.

2.6.5 Modifiable risk factors

- BMI has been examined in only one study and no association has been found (186).
- Cigarette smoking (former and current) has been associated with GCA with odds ratios ranging from 1.29 to 6.32 (180, 187, 188). For PMR there has been one case-control study identified smoking as a risk factor but only in women OR of 3.64, 95% CI 1.07-12.40 (189).
- Lower socioeconomic status showed a positive association with a risk of visual ischaemic complications associated with GCA in one study (190).
- Cardiovascular disease was shown to be a risk factor for GCA but only in women (191).
- Peripheral vascular disease has been associated with PMR but findings are inconsistent (192).
- There have been no studies assessing dietary factors

- Multiparity was associated with a reduced chance of GCA diagnosis from one study (193).
- Pharmacological influences: several retrospective case-series studies and one case-control study have assessed the effect of statins on GCA incidence and complications (including relapse rates, risk of blindness, and mortality). These studies showed decreased risk of GCA in those individuals taking statins (OR 0.31 95% CI 0.15 to 0.6), but no change in the disease outcomes or mortality (194-197).

2.6.6 Comments

Most of the studies investigating risk factors were of case-control design with problems of recall bias for exposures, and difficulty in finding representative control groups. In addition most cases comprised hospital-treated patients, leading to difficulties of generalisability to other groups, particularly those treated in the community who may display a different phenotype and have an alternative morbidity profile. There have been relatively few studies, which have assessed risk factors for disease progression, namely visual loss associated with GCA and inflammatory polyarthritis associated with PMR.

2.6.7 Risk factors for ocular morbidity

To date, risk factors for visual loss have been studied mainly amongst cohorts of patients from single centres. The literature shows an

association between laboratory markers and subsequent blindness: greatest risk is associated with relatively lower inflammatory markers at diagnosis, anaemia and thrombocytosis as well as constitutional symptoms (58, 198, 199). Comorbidity is also associated with visual loss in GCA, with hypertension and ischaemic heart disease implicated as increasing the risk of blindness (188, 198, 199).

However not all studies confirm an association between cardiovascular risk factors and ischaemic manifestations, including ocular morbidity in GCA. A multi-centre retrospective study of 271 cases of GCA in the UK, reviewed contemporaneous patient care records for the presence of ischaemic complications: of these, 222 (81.9%%) had ischaemic manifestations, of whom 100 had transient visual loss, and 46 (17%) suffering irreversible visual loss (190). Also recorded were data on hypertension (on anti-hypertensive agents or BP > 140/90 mmHg on two or more occasions), atherosclerosis (clinically recorded myocardial, cerebral or limb ischaemia not directly attributable to GCA), deprivation (index of multiple derivation 2007), smoking (current, former, never) and duration of symptoms prior to treatment with glucocorticoids. After adjustment for age and sex, neither hypertension nor atherosclerosis were associated with irreversible ischaemic complications (irreversible visual loss including; limb arterial stenosis n=6, irreversible diplopia n=5, stroke n=3, and myocardial infarction n=1) (190). However, logistic regression analysis comparing the most-deprived with the least-deprived quartile resulted in an odds ratio of 3.0 (95% CI 1.1, 7.9; p=0.029)

(190) which the authors concluded was partly due to delays in presenting to medical services for treatment. Statins prescribed prior to diagnosis of GCA appeared to have little effect on those who subsequently develop ischaemic manifestations, compared with those not on statins OR for ischaemic manifestations 0.74 (95% CI 0.34, 1.62; p=0.46). Although prescription of aspirin was associated with an increased odds ratio for ischaemic manifestations OR = 2.81 (1.06, 7.45; p=0.038) (190), it is important to note that as these were unadjusted odds ratios, this result may have been biased through confounding by indication. No propensity score matching was attempted.

A Swedish study using the Skåne Healthcare Register identified 840 patients with temporal artery biopsy-positive GCA diagnosed between 1997 and 2010. International Classification of Disease tenth edition (ICD-10) codes for visual complications recorded in GCA cases were matched (in a nested case-control analysis) to one control (without ICD-10 recorded visual complications) on the basis of calendar year of birth (+/- five years), sex and year of diagnosis (200). A second analysis using a matched-cohort design, matched all 840 cases of GCA (age, sex area of residence and index year) to four randomly selected controls without a diagnosis of GCA, in order to calculate rate-ratios for visual impairment. Follow-up time was from date of index case to either date of visual ICD-10 code entry, death or end of follow-up period (31st December 2011) (200). Using logistic regression, several medications and their association with visual impairment were analysed. A review of the case notes

revealed 85 cases (10.1%) with ICD-10 codes for visual impairment following their diagnosis of GCA: 18 patients (2.1%) had complete visual loss, two of whom with binocular visual loss (200). The rate ratio for ICD-10 coded visual complications compared with the matched controls was 3.0 (95% CI 2.3, 3.8; p=<0.001) (200). Logistic regression analysis in the nested case-control analysis revealed an univariate odds ratio of 2.77 (95% CI 1.29, 5.95; p=0.009) for ICD-coded visual complication and beta-blockers which increased to 6.98 (95% CI 1.29, 37.8; p=0.02) once headache, fever, abnormal temporal artery on clinical examination, presence of PMR, and ACE-i prescription were included in the model. In keeping with the UK study, no attempt was made to address confounding by indication due to beta-blockers and their use in treating cardiovascular disease.

2.6.8 Risk factors for inflammatory arthritis following a diagnosis of PMR

The relationship between PMR and inflammatory polyarthritis (IP) remains a source of debate: although they have been classified as two distinct entities, they share many clinical features (33, 201-203). It remains unclear as to whether synovitis is part of a spectrum of PMR, or if the symptoms of PMR are early manifestation of rheumatoid arthritis (RA). Alternatively the development of synovitis might represent a phenotypic transformation in susceptible individuals.

Studies conducted in secondary care suggest that patients initially diagnosed with PMR develop IP within twelve months of diagnosis (17, 204, 205) with the presence of peripheral small joint synovitis, at time of PMR diagnosis, the most consistent risk factor. The greatest risk of diagnostic switch shown is from a single centre self-referred study of 62 patients with PMR from the USA, with 52 (84%) developing synovitis in who were diagnosed with rheumatoid arthritis (RA) within an average of nine months from their PMR diagnosis date (33).

2.7.0 EVIDENCE GAPS

There is wide variation in the published incidence and prevalence estimates for PMR and GCA with few studies involving community-based patients.

The is a genetic contribution to both diseases particularly involving MHC-Class II but other cellular processes including immune cell signalling and vascular remodelling, although none fully explain the reasons for disease development (206). Since the majority of published data on risk factors for PMR and GCA development are based on cross-sectional case control studies conducted in a hospital setting, and so prone to selection bias and difficultly in establishing causation, interpretation is problematic.

Population data from registries (for example the Ontario Health Insurance Plan, UK-based CPRD, and Scandinavian disease registries) are limited by problems of case ascertainment, disease definition and validation, since

diagnoses are recorded by GPs pragmatically and therefore researchers are unable to apply classification criteria. No study has captured risk data prior to disease onset.

There are no accurate data either on the incidence and significance of sub-clinical ocular involvement, or the risk of progression of eye disease over time, nor has an evaluation been made of the relative frequency of eye morbidity related to treatment. Therefore there is difficulty in gauging the true risk of eye complications in PMR and GCA. The factors which might predict the onset and progression of eye disease in GCA are unknown, and there is little understanding of how best to monitor patients over time for the development of eye disease over time.

It is important to distinguish clinically the nature of IP following a diagnosis of PMR and may help identify patients who might benefit from the early introduction of disease-modifying drugs (DMARDs). However, problems arise interpreting the studies to date because of the potential influence of referral and diagnostic suspicion bias inherent in hospital-based series as well as small samples sizes and relatively short follow-up intervals. Longer duration studies need to take account of mortality in what is an older patient population.

2.8.0 THE NEW DATASETS

The limitation of small hospital series can be overcome by large datasets that have recently become available. However, the problems outlined

around definition of cases and requirement of community-based populations needs considerable effort in order to generate analysable data. The new datasets used in this thesis are outlined below with further in-depth description on participant recruitment and case ascertainment and definitions provided in the subsequent Methods chapter. The brief section below gives an overview of the considerable effort in order to achieve the desired outcome of a robust community-derived data source in order to study the epidemiology of PMR and GCA, with more detailed description in the Methods and Results chapters.

2.8.1 GCANS – Giant cell arteritis in Norfolk Study

To provide a community-based survey population, the GCANS project was set-up at a large two-site Norfolk general practice. GCANS's objectives were to ascertain community-derived estimates of occurrence, and understand the frequency of clinical features associated with PMR and GCA within the population.

The most recent prevalence for PMR and GCA for the UK was published in 1985 by Kyle et al (112), within a single general practice of 5,500 patients, with 650 (11.8%) aged 65 years or older. All were interviewed, with those with responses suggestive of PMR or GCA undergoing venesection for ESR testing, with those having an ESR of 30 mm/hr or greater being reviewed clinically, with those meeting the Jones and Hazleman criteria considered to have PMR and or GCA. The most recent

census data available for Norfolk reveal that 25.7% are aged 65 years or older, over twice as many compared to the Kyle et al study.

To update the community-based prevalence estimates for both PMR and GCA, case record review was used, supplemented by population survey via questionnaire and subsequent clinical examination by a rheumatologist, similar to the approached used by Kyle et al. Practice case records at the surgery were reviewed and in addition a population survey was undertaken to capture any unknown or undiagnosed cases of PMR or GCA within the practice population.

Despite its relatively small size (n=5,159) this project was strengthened by the use of the population survey, clinical review and access to haematological and biochemical test results, with more detail given in chapters 4.2.0 and 5.1.0.

Full ethical approval was granted from Norwich Research Ethics Committee, with participants giving written informed consent.

2.8.2 PMR and GCA in EPIC-Norfolk

For 20 years epidemiologists have focused on the Norfolk population to study common chronic diseases because of its relative stability, with little outward migration. Healthcare is mostly sought within the region, with the most encountering secondary care at a single central hospital (Norfolk and Norwich University Hospital). All the processing of

haematological, biochemical and pathological samples is carried out within the hospital's laboratory. The Norfolk Arthritis Register has provided definitive data on the incidence of inflammatory arthritis and RA within this population. Similarly the Norfolk Vasculitis Register has provided data on the incidence of rare vasculitides (207, 208).

Norfolk is also a site for the UK centre for the European Prospective Investigation into Cancer (EPIC). EPIC-Norfolk is a cohort of 30,445 men and women resident in East Anglia, aged 40–79 years, between 1993 and 1997). Participants from 35 GP practices and have taken part in serial screening assessments which included measures of nutritional and environmental exposures. Initially set up to study the aetiology of cancer, in subsequent years the study has been broadened to include chronic diseases.

Extensive work was needed to set-up and identify participants within EPIC-Norfolk who had been diagnosed with PMR and GCA in order to take advantage of what could be a rich data source with fine granularity. A more detailed description of the process involved is given in the Methods (4.3.0) and Results (5.2.0) chapters.

The eye data captured as part of the EPIC eye study are particularly valuable for PMR and GCA studies. This cohort of a total of 8,623 participants aged 48–92 years have undergone extensive eye testing including retinal digital imaging. Examination of retinal blood vessels offers an opportunity to view and image the circulatory system directly.

In patients with GCA, typical histopathologic changes in affected arterial segments include inflammatory cell infiltrate, with or without the presence of giant cells, reduplication of the intima and fractures of the internal elastic lamina. The inflammatory cell infiltrate is from the adventitia towards the lumen and is focused around dendritic cells within the arterial wall. No venous pathological changes are reported in patients with PMR or GCA which may be due to the lack of dendritic cells in the vessel walls of veins. However, peripheral vascular disease is reported in patients following their diagnosis of PMR and / or GCA, but the biologic mechanisms and process of this association have yet to be clarified.

Few autopsy studies have charted the anatomical involvement of arteries in GCA (see Table 2.1). Most frequently affected are the large arteries, particularly the aorta and its superior branches, the subclavian, common carotids, internal carotid and ophthalmic artery and its branches. Involvement of the arterial supply to the eye may lead to the most feared complication in GCA of blindness, most commonly through the consequence of anterior ischaemic optic atrophy, affecting around 1/12 patients with GCA. More frequent is less severe visual impairment but the estimates vary widely. It is unknown whether typical histopathological changes of GCA affect the retinal vessels.

Vasculitic changes may affect the retinal arterioles in patients with GCA and detailed ophthalmological reports reveal relatively thin arteriole vessels in affected patients. Of greater interest to study may be the nasal

vessels due to their close proximity to the disc and the fact that retinal artery involvement has been reported (See Table 2.1 for details). Additionally, the presence of anomalies such as ciliary retinal arterioles may be of interest since they are derived from the posterior ciliary vessels, more frequently affected in patients with GCA (209). Any findings found by manual grading could be used in a validity assessment against the QUARTZ (automated processing software – more detail given in section 4.5.3) produced data. In addition an atlas of changes could be derived.

2.8.3 Diagnosis and Classification Criteria in Vasculitis Study (DCVAS)

This study used participants recruited into the Diagnosis and Classification Criteria in Vasculitis Study (DCVAS), an international register capturing demographic and detailed clinical information from consecutive patients with vasculitis from around the world, presenting to clinic-based physicians. Reasons for referral, clinical signs and symptoms present at the time of clinical review are recorded. A detailed description of the DCVAS dataset and the definitions of disease are given in the Methods chapter section 4.4.0.

2.8.4 Advantages of the datasets

The use of the above data sources for the purposes of studying the epidemiology of PMR and GCA has potential for significant advances in

the knowledge base. The creation of a community-based cohort allows for a robust assessment for both incidence and prevalence estimates. Extending the EPIC-Norfolk cohort to PMR and GCA provides the significant advantages of a prospective cohort study in order to investigate the aetiology of both conditions from community-treated patient populations. The problems of recall bias and unrepresentative control groups from previous case-control work will be negated by the use of a prospective cohort. The investigation of factors associated with blindness from the large international DCVAS will produce estimates which should have much greater value in terms of generalisability compared to the small studies from single centres to date. Updated community-based estimates for disease incidence and prevalence will allow for great understanding of the public health consideration required.

2.8.5 Thesis originality

There are identified evidence gaps and uncertainty in the published estimates regarding the descriptive epidemiology of these two important related conditions warranting further scientific endeavour. The prospective and community-based features of the EPIC-Norfolk cohort are fundamental to the originality of this work. In addition establishing GCANS is important in order to derive modern estimates, based on current classification criteria for the diseases of interest. The most novel aspect of this body of work is the use of retinal fundal images to assess for vascular changes, either morphological associations of disease or robust indicators of end organ damage associated with hypertension.

CHAPTER 3 AIMS

3.0 SUMMARY

This chapter sets out the overall justification and purpose for the thesis, detailing the broad and specific aims of this work.

3.1.0 Aims and purpose.

The broad aims for this thesis are to update incidence and prevalence estimates for PMR and GCA from community treated patients, using accepted definitions of disease and ability to apply current classification criteria. In addition, rates of disease progression associated with GCA and PMR will be reported, with investigation of risk factors for blindness in GCA and inflammatory polyarthritis in PMR.

The specific aims are as follows:

- provide definitive data on the absolute rate of occurrence of PMR and GCA and the risk of associated ocular complications
- assess key risk factors for disease onset and progression: the thesis will address a number of specific aetiological hypotheses assessing previously reported risk factors, including both non-modifiable and modifiable factors:
    - Smoking is associated with an increased risk for both PMR and GCA.

    - Traditional cardiovascular risk factors (hypertension, hypercholestrolaemia, diabetes, high BMI) are associated with an increased risk for both PMR and GCA.
    - Statins are associated with a reduced risk for PMR and GCA and in addition a favourable disease course with reduced morbidity.
    - Subsequently to investigate other commonly prescribed mediation including anti-hypertensive agents.
    - Multiparity is associated with a decreased risk for later PMR and GCA development.
- examine ocular outcomes in PMR and GCA to establish the rate of occurrence and significance of subclinical vascular retinal disease, and to assess these complications with the use of digital retinal images

CHAPTER 4 SUBJECTS AND METHODS

4.0 SUMMARY

This section provides a summary of three datasets analysed for this project comprising a community-based cohort from a single GP practice, a prospective cohort study – the European Investigation into Cancer and Nutrition Study (EPIC-Norfolk), and a large international consortium – Diagnosis and Classification criteria in Vasculitis Study (DCVAS).

The chapter includes details of the recruitment of participants, how individuals were ascertained and then defined as having the disease of interest. Analytical methods used to calculate prevalence, incidence and to investigate aetiological factors are discussed.

A novel aspect of this project was the use of fully automated software to generate measure of retinal vessel widths and the manual review of retinal fundal images to record morphological features. The process involved as part of this review is described in detail.

4.1.0 Overview of the Data

The limitations of existing data have been discussed in the Chapter 2, foremost of which are the use of selected often clinic based populations and small sample sizes. Where large dataset have been used often classification sets have not to define disease.

The three datasets that form the basis of this study address these issues and comprise GCANS, EPIC-Norfolk and DCVAS. They are used to firstly address the descriptive epidemiology, namely providing up to date estimates of incidence and prevalence of PMR and GCA and the complications of visual loss in GCA and inflammatory arthritis in PMR and to estimate aetiological factors involved in the development of disease and outcomes.

4.2.0 COMMUNITY-BASED SURVEY - GCANS

GCANS (Giant Cell Arteritis and polymyalgia rheumatica in Norfolk Study) was conducted at a large dual site general practice in Norfolk on the outskirts of Norwich providing care for approximately 13,000 individuals, which includes urban and rural areas, residential suburbs and extends into outlying villages. Case ascertainment comprised GP record review supplemented by postal survey and selected clinical examination.

4.2.1 GP case record review

Cases of PMR and GCA were identified through a GP database review, including all individuals aged ≥ 55 years. The electronic GP register was interrogated using Read code analysis (GCA: G755., G7550, G7551, G7552, G755z and PMR: N20.., N200.) and key word searches (polymyalgia rheumatica, giant cell arteritis, temporal arteritis). In order to satisfy a GP diagnosis of either GCA or PMR, patients needed to have received treatment with glucocorticoids *and* a diagnosis that was not later

refuted. Those whose diagnoses were later refuted were considered not to have the conditions.

4.2.2 Supplementary postal survey

No questionnaire exists for diagnosing patients with PMR or GCA so one was required, sensitive to the cardinal features of PMR and GCA. In order to capture undiagnosed cases, the questionnaire needed to be sensitive to the detection of the broadest possible range of symptoms of PMR and GCA. The diagnosis could later be confirmed or refuted by applying clinical judgement during a patient visit. By adapting the 1985 questionnaire used by *Kyle et al*, a new questionnaire was developed to include the 1990 American College of Rheumatology (ACR) criteria set for GCA (210) and informed by a review of the nature and frequency of symptoms reported from PMR and GCA cohorts published in the literature. This new questionnaire captured the following symptoms: shoulder pain and stiffness, myalgia, weight loss, general malaise, headache, visual disturbance, scalp tenderness, symptoms suggestive of jaw claudication, and important potential discriminative symptoms of migraine; participants were also asked whether they had ever been diagnosed by their GP with either PMR or GCA. Its face validity was confirmed in a hospital sample of ten patients with PMR and or GCA, and among three rheumatologists and two rheumatology nurse practitioners specialising in vasculitis (see Appendix 1).

The postal questionnaire was sent to all patients registered with the practice over the age of 55 years old. Exclusion criteria included patients with dementia, a terminal illness, were living in a nursing home or who had previously informed the practice they did not wish to take part in research. Non-responders were sent a reminder invitation and another questionnaire after three months.

4.2.3 Clinical review of potential cases

All participants who answered positively to questions on jaw claudication AND scalp tenderness AND visual disturbance, with or without the presence of headache and who were not already known to the practice as having a diagnosis of GCA were invited for clinical review by a rheumatologist (the author). This group was considered as having a high likelihood of having a diagnosis of GCA. Those answering positively to one or more questions were considered at intermediate likelihood of having PMR or GCA. A random sample (*Excel Microsoft Corporation* random number generator) of these was invited for clinical review, included in which potentially undiagnosed cases of PMR or GCA would be expected.

4.2.4 Case definition

Following the process of cases ascertainment, cases of PMR and GCA were defined as those cases with a diagnosis of either PMR or GCA in the

GP electronic record who had received treatment with glucocorticoids and in whom the diagnosis had not been later refuted.

Secondly as part of a sensitivity analysis, those cases of PMR subsequently fulfilling the common criteria sets are presented (See Table 2.2) although due to the lack of testing for rheumatoid factors and anti-CCP antibodies cases will not be scrutinised by the current EULAR/ACR criteria. Cases of GCA will be analysed using the 1990 American College of Rheumatology (ACR) classification criteria (210) (see Table 4.1).

Table 4.1 The 1990 ACR classification criteria set for GCA

1. **Age** at disease onset >=50 years (Development of symptoms or findings beginning at age 50 or older)
2. **New headache** (New onset of or new type of localized pain in the head)
3. **Temporal artery abnormality** (Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries)
4. **Elevated erythrocyte sedimentation rate** (Erythrocyte sedimentation rate >=50 mm/hour by the Westergren method)
5. **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)

For purposes of classification, a patient shall be said to have giant cell arteritis if at least three of these five criteria are present. The presence of three or more criteria yields a sensitivity of 93.5% and a specificity of 91.2% (210).

4.2.5 Sample size and analytical approach

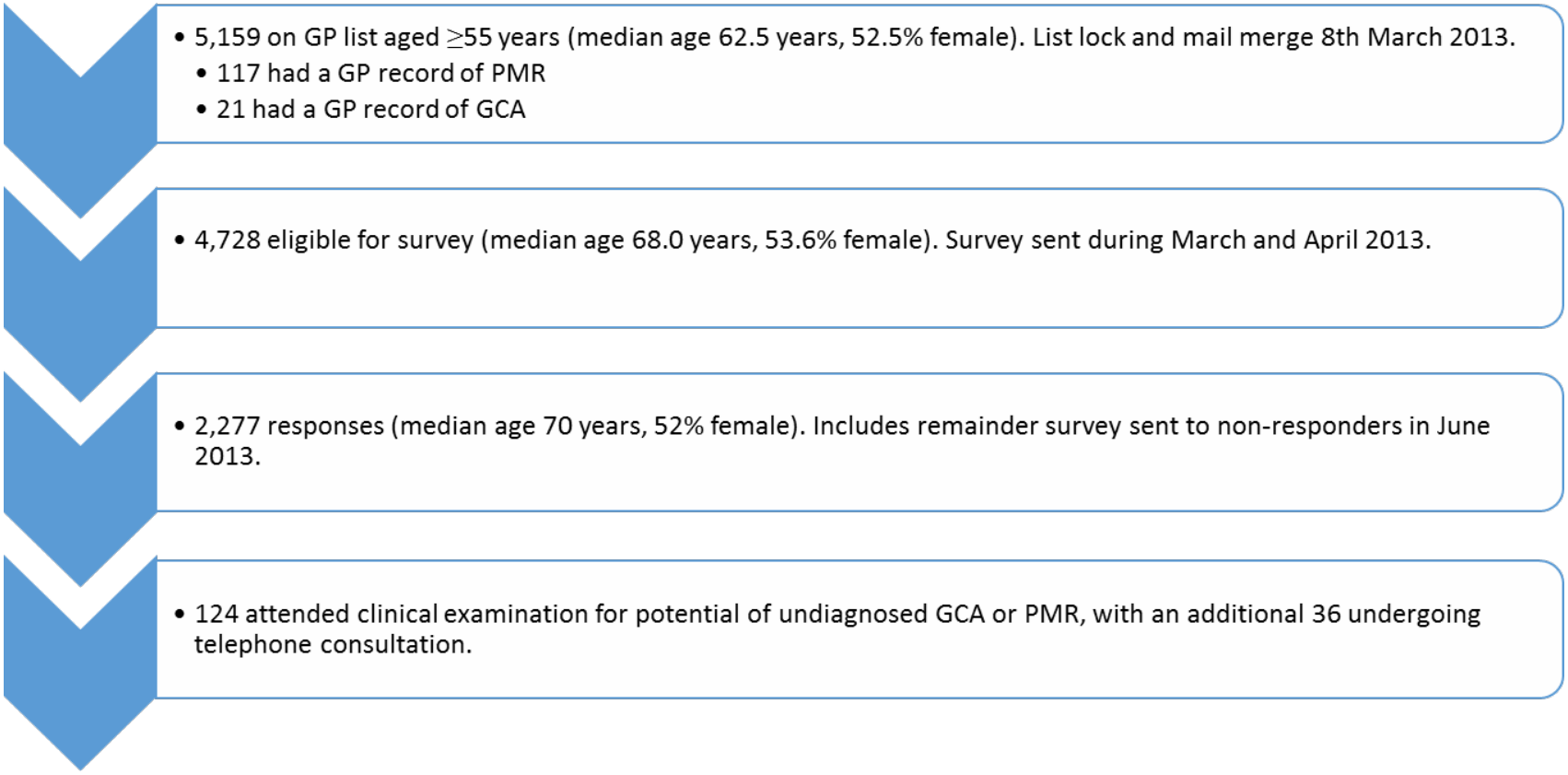
Minimum cumulative prevalence estimates were calculated for both diseases. This method assumes that all known cases are identified, those who died within the population, prior to the end of the follow-up period, are excluded and that non-responders to the survey do not have the disease of interest and contribute to the denominator. Cumulative prevalence estimates were expressed as a proportion; confidence intervals were calculated based on the Poisson distribution.

The five electoral wards covered by the practice have a combined population (from the 2011 Census) of 15,102 of whom 5,108 (34%) were aged ≥55 years and 2,983 (20%) were aged ≥65 years. The practice is representative of the Norfolk population in terms of ethnicity, gender ratio and age structure (36% of the Norfolk population are aged ≥55 years). A sample size of 4,000 allowed the detection of an anticipated prevalence of 0.3% for GCA with 95% confidence interval ranging from 0.13% to 0.47%. A greater level of precision would be possible for PMR as it is more common than GCA.

4.2.6 Participant flow

The number of participants involved in the GCANS study is displayed in Figure 4.1

Figure 4.1 Participant flow chart for GCANS



4.3.0 EPIC-NORFOLK

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a large prospective cohort set up in the 1990s across 10 European countries, recruiting around half a million individuals and EPIC-Norfolk represents one of the recruitment areas (in Norfolk, UK). Individuals were recruited from 35 GP practices across rural, sub-urban and inner city areas. A total of 30,445 men and women were consented with 25,639 participants, aged 40-79 years, recruited between the years 1993-1997 (211).

The cases of PMR and GCA need to be identified and clinical information scrutinised in order to carry out case ascertainment and definition.

During baseline nurse-led health check clinics and by using validated questionnaires, participants provided detailed information on demography, height, weight, smoking and alcohol intake. The Norfolk Health Authority granted ethical approval at the time of study set-up, with subsequent revisions over the past 25 years.

4.3.1 Case ascertainment

Three methods were used to identify incident cases of PMR:

1. Potential cases of PMR using ICD 10 codes (M35.3 and M31.6, PMR and GCA with PMR respectively). This identified those patients who had a referral to secondary care and had been diagnosed with

PMR, either following a direct referral for suspected PMR or if mentioned within their previous medical history.

2. Potential cases from out-patient clinic letters using a keyword search with Boolean operators for "polymyalgia" and "rheumatica" in letters from clinicians based in geriatrics, ophthalmology, neurology or rheumatology.
3. EPIC-Norfolk follow-up questionnaires: Q12 enables participants to provide free text information on diagnosis occurring after the baseline questionnaire. This was sent to participants at baseline, three, five and ten year follow-up.

Four methods were used to identify incident cases of GCA:

1 Potential cases of GCA using ICD 10 codes (M31.5 and M31.6, GCA and GCA with PMR respectively). This identifies those patients in the EPIC cohort who have had a referral to secondary care and subsequently diagnosed with GCA.

2 Potential cases from out-patient letters. This was based on a keyword search with Boolean operators for "arteritis" OR "giant" in any clinic letters from clinicians based in geriatrics, ophthalmology, neurology or rheumatology.

3 Participants in EPIC who have had a temporal artery biopsy using operating procedure code (OPCS) L67.1 (temporal biopsy).

4 From EPIC-Norfolk follow-up questionnaires: Q12 enables participants to provide free text information on diagnosis

occurring after the baseline questionnaire. This was sent to participants at baseline, three, five and ten year follow-up.

This has found 712 potential cases of PMR and / or GCA (516 participants with PMR, 196 participants with GCA).

4.3.2 Hospital records review

The classification sets for PMR and GCA require results of blood tests and for GCA, results of temporal artery biopsy. These criteria were then applied to potential cases of PMR and GCA identified from the cohort.

As part of the agreement with practices in EPIC-Norfolk, direct access to GP records is not permitted. However, 94.9% of outpatient visits for EPIC-Norfolk participants occur at the Norfolk and Norwich University Hospital, which performs biochemical and haematological laboratory assessment for all primary or secondary-care based clinicians. Therefore even where a GP had exclusively managed their patient with PMR or GCA in the community, it is possible to gain access to any patient blood test results.

4.3.3 PMR case definition

There are several sets of diagnostic and classification criteria for PMR, which include both clinical features and biochemical factors [37-40] with inflammatory markers (CRP or ESR), age > 50 years and bilateral shoulder pain common across the published criteria. For the purposes of

this study individuals who self-identify as having PMR on the EPIC questionnaire *and* are treated as such by their GP with at least six months of steroid therapy *and* have raised inflammatory markers (CRP >6 mg/L and / or ESR >40 mm/hr) *and* are aged >50 years at time of diagnosis will be considered to have the condition and are referred to PMR50 from now on in the text. Secondly, as part of a sensitivity analysis, those cases of PMR subsequently fulfilling the European League Against Rheumatism / American College of Rheumatology (EULAR/ACR) classification set for PMR will be analysed.

4.3.4 GCA case definition

For the purposes of this study, individuals who self-identify as having GCA on the EPIC questionnaire *and* are treated as such by their general practitioner with at least 6 months of steroid therapy *and* are aged >50 years at time of diagnosis will be considered to have the condition are referred to GCA50 from now on in the text.

Secondly as part of a sensitivity analysis, those cases subsequently fulfilling the 1990 American College of Rheumatology (ACR) classification criteria (210) (see Table 5.4) will be analysed. The criteria are based on clinical, biochemical and histological features of the disease.

4.3.5 Baseline exposures recorded for the EPIC cohort

- Smoking status – divided into current, former and never categories.
- BMI (kg/m^2) – set for standardised categories as defined by the World Health Organisation.
- Diabetes mellitus (both Type I and Type II) – those with / those without at the time of recruitment.
- Hypertension – those on medication for hypertension / those not
- Alcohol consumption – measured in the food frequency question divided into standardised categories.
- Dietary fatty acids divided into quintiles of dietary intake from seven day food diaries.
- Medication at the time of recruitment – statins and hypertensives were chosen to be included in the analysis from the previously published data.
- High-sensitivity CRP measured at the first health-check

The data were collected at the first health check, with CRP measured on serum blood samples using the Olympus AU640 assay, able to measure high-sensitivity CRP over the range of 0 to 160 mg/L (212).

4.4.0 INTERNATIONAL CONSORTIUM OF VASCULITIS - DCVAS

This study used participants recruited into the global Diagnosis and Classification Criteria in Vasculitis Study (DCVAS), which captures consecutive patients presenting to clinic-based physicians.

4.4.1 Case recruitment and setting

DCVAS was set-up in 2010, recruiting patients from 129 sites worldwide (see Figure 4.2).

Figure 4.2 DCVAS recruitment

The purpose of DCVAS is to develop and validate diagnostic and classification criteria for systemic vasculitis for use in daily clinical practice and in clinical trials. Physicians recruit patients with diagnoses of

vasculitis or comparator conditions at the time of diagnosis. Information collected includes clinical, serological, pathological and radiological data and records demographic and detailed clinical information, reasons for referral and clinical signs and symptoms present at the time of clinical review.

4.4.2 Case ascertainment and definition of GCA

The DCVAS protocol required the examining physician to submit an assessment of their level of diagnostic certainty (very certain, ≥75%; moderately certain, 50-74%; uncertain, 25-49%; very uncertain, <25%) for each participant at baseline and after six months. Musculoskeletal features were also recorded including whether patients had a prior diagnosis of polymyalgia rheumatica. Inclusion criteria were a new baseline diagnosis of GCA (i.e. not relapsing disease), which was confirmed after six months with a confidence level of ≥75%. The results of temporal artery biopsy (TAB) were also available, allowing patients to be classified using the 1990 ACR criteria set for GCA (210). A positive TAB was defined as the presence of inflammatory cell infiltrate and / or presence of giant cells in line with 1990 ACR criteria.

4.4.3 Previous medical history

For all patients the DCVAS protocol records specific medical conditions present before the onset of the current illness, including coronary heart disease, heart failure, peripheral vascular disease, hypertension requiring

medication, chronic obstructive pulmonary disease, asthma, diabetes mellitus, cerebrovascular accident, dyslipidaemia and malignancy. In common with many large registry datasets, these diagnoses were defined, a physician-recorded entry in the patients' care record.

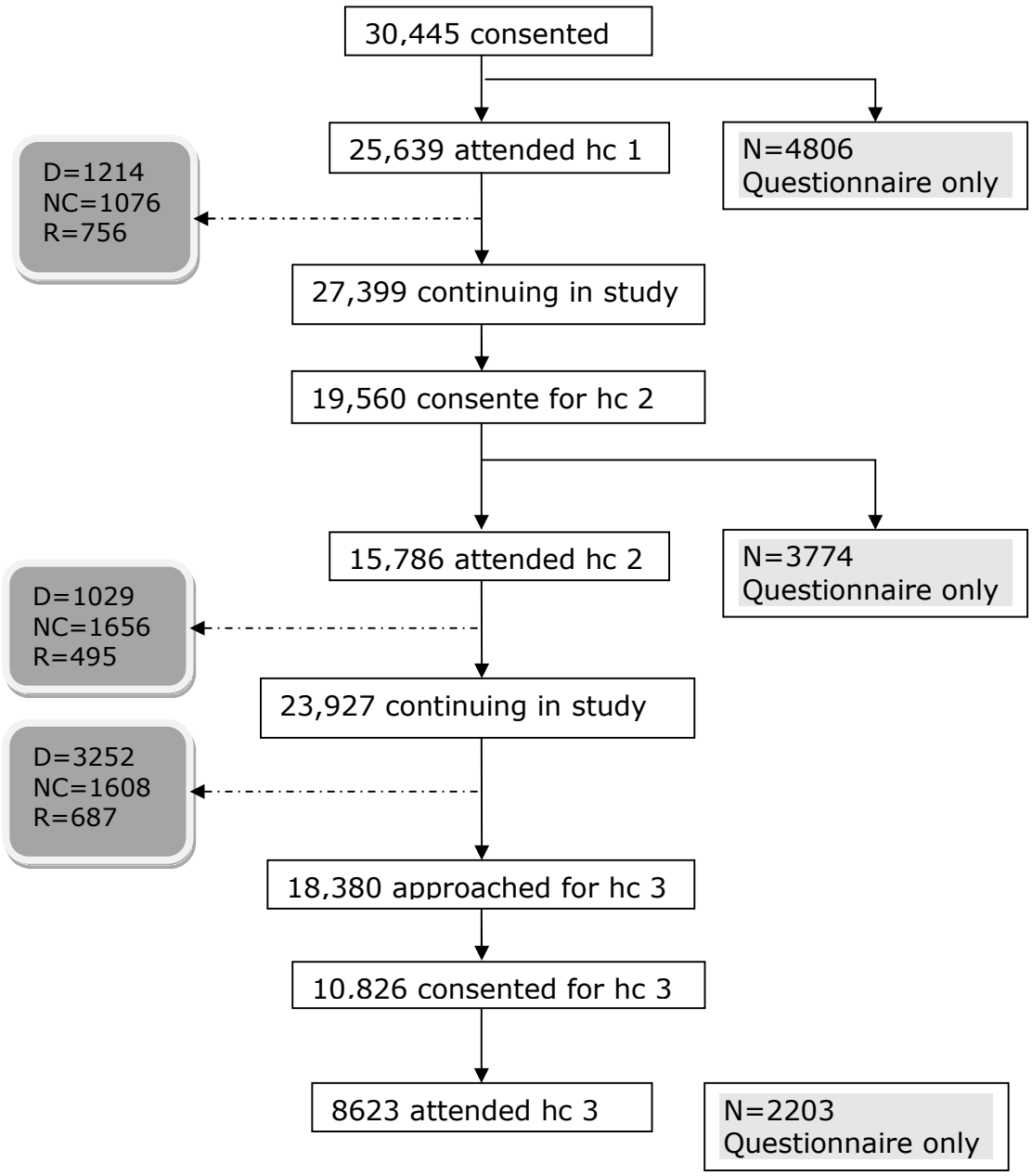
4.4.4 Definition of blindness

The Vasculitis Damage Index (VDI) was used to assess new onset blindness, defining blindness in one or both eyes as complete loss of vision (213). Also recorded at baseline were data on ophthalmic features (amaurosis fugax – transient monocular blindness, sudden ongoing visual loss – loss of vision either visual field defect or blindness, blurred vision, or diplopia – double vision). VDI records diplopia and visual impairment as a single item but this was not included as a primary outcome measure due to the lack of consistency in definition and potential for misclassification bias.

4.5.0 EPIC-Eye Study

A total of 8,623 participants aged 48-92 years attended the Eye Study (nested within EPIC-Norfolk, carried out between 2004-2011) as part of the third health check, and underwent assessment of visual acuity, autorefraction, biometry, tonometry, corneal biomechanical measures, scanning laser polarimetry, confocal scanning laser ophthalmoscopy, fundal photography and automated perimetry (214). See Figure 4.3 for numbers of participants attending the health checks.

Figure 4.3 Flow diagram of EPIC-Norfolk participants



D –death, NC – not contacted, R – refused, hc *n* – health check number.

This third health check occurred between the years 2004 to 2011, roughly a midway point between initial participant recruitment (to EPIC-Norfolk) and the present day. Therefore it is to be expected that approximately half of the participants with either a diagnosis of PMR or GCA will have had their third health check prior to their diagnosis of PMR or GCA. This allows for examination of both aetiological and long-term sequelae hypotheses in respect of retinal morphological changes.

4.5.1 EPIC-Eye visual acuity assessment

Habitual (that is uncorrected by glasses or contact lenses) monocular visual acuity (VA) was measured using a logarithm of the minimum angle of resolution (LogMAR) chart (Precision Vision, LaSalle, Illinois, USA) with the aid of the participants' available distance correction at 4m (or 2m then 1m if unable to read any letters). VA for both eyes was recorded.

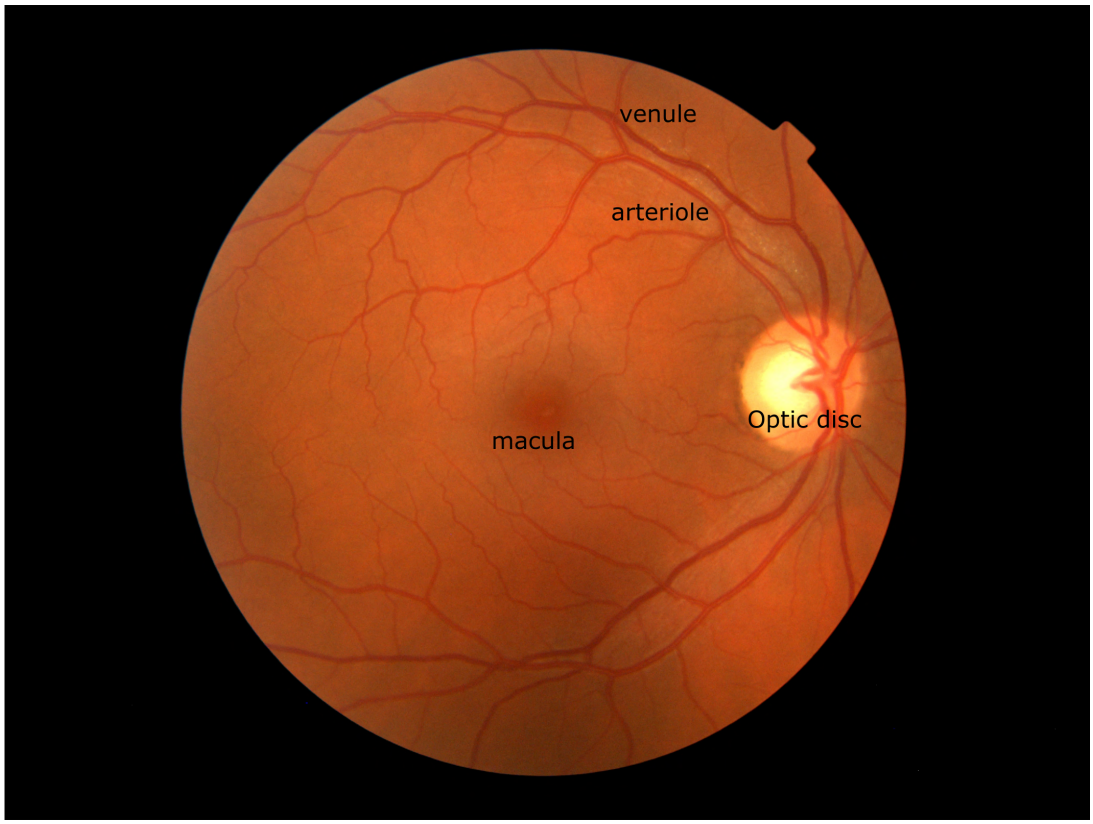
WHO defines low vision as worse than 0.5 LogMAR but equal or better than 1.3 LogMAR in the eye with the best vision, or visual field loss corresponding to less than 20 degrees in the better eye. Blindness is defined as either LogMAR equal or greater than 1.3 or visual field of 10 degrees or less around central fixation in the eye with best vision. Visual impairment includes both blindness and low vision. LogMAR values corresponding to counting fingers (CF), hand movements (HM), perception of light (PL) and no light perception (NLP) were substituted as LogMAR, 2.10, 2.40, 2.70 and 3.00 respectively (215).

Blindness associated with GCA is often unilateral and therefore visual impairment for left and right eyes as well as for the total number of participants affected is reported.

4.5.2 Retinal fundal images

The EPIC Eye study participants had numerous measures related to eye health recorded, including measures of visual acuity and digital retinal photographs and analysis of these retinal photographs forms a significant proportion of the work in this thesis. Non-mydratic images were taken using a TRC-NW65 Topcon fundus camera with a 45 degrees field-of-view. The participants had photographs of both left and right eyes, sometimes with each eye being photographed more than once. The images are centred on the fovea, typical for the diabetic retinopathy screening programme (see Figure 4.4 for an example of a retinal image – source UK Biobank).

Figure 4.4 Retinal fundal image



Retinal fundal image of a right eye. Image from UK Biobank (© UK biobank). Macula centred image. The optic disc on the right shows a bright white centre called the optic cup. The central retinal reflex can be seen as a white line in the arterioles.

4.5.3 QUARTZ

In collaboration with researchers based at St George's Hospital and Kingston University, a software program called QUARTZ (Quantitative Analysis of Retinal Vessel Topology and size) has been developed to measure retinal vessel widths. It is able to process digital retinal images, identify the optic disc location and characterise the vessels into arterioles and venules and measure vessel widths.

The QUARTZ program was developed due to the need for a fully automated system able to process large numbers of retinal images for the purposes of epidemiological research (216). The program is able to record:

- Left or right eye (via location of the optic disc in macula centred images)
- Classification of vessels into arterioles and venules
- Vessel segmentation
- Centreline coordinates of vessel segments
- Vessel widths at each centreline coordinate

Developed in Matlab, the software uses a multi-scale line detector using average grey-level of each pixel (216). The average pixel intensity is measured along lines of a certain length in 12 different planes spaced at 15 degrees. The line with the highest average pixel intensity is selected, then the process repeats for different line lengths and the final line

placement based on the highest average grey value of a square sub-window centred at the target pixel to identify the central vessel reflex. The algorithm then performs hysteresis morphological reconstruction to produce a line strength image (LSI). The LSI has two levels of grey-value threshold applied to it in a two-step process. Firstly the threshold is selected at a narrow threshold range for the high object confidence pixels (those with the greatest value for grey-value or brightness). The resultant image is named as a marker image and includes the vessels and false negatives. A second threshold is then applied, which has a wide threshold range to the greyscale image. Centre lines of the vessels are then applied to the image with those pixels with the brightest intensity selected. Vessel segments are then devised from the centre-lines with a thinning operation, whereby spurs (<10 pixels), short segment lengths (<15 pixels) and cross-over or bifurcation points are removed (217).

The QUARTZ program classifies vessel segments into two groups of either arteriolar or venular. It uses an ensemble classifier of bagged decision trees based on colour features of each segment. The decision tree uses three parameters: the central line pixel intensity, the variation in the brightness of the pixels away from the centre-line and the variation in pixel intensity along the segment in order to make judgements on the probability that the segment in question is an arteriole or venule. The intensity of each pixel is calculated in each of the Red, Green, Blue (RGB) colour and Hue, Saturation, Intensity (HIS) channels. Through training

rounds of the classifier algorithm it was established that 16 is the optimum number of decision trees used for vessel classification (218).

Finally, measures of vessel width are determined using a Gaussian function. The central line of the vessel has the brightest value with a dropping in the intensity further away from the centre line. The inflection points of the Gaussian curve are calculated which correspond to the vessel edges (219). The resultant output produces measures of vessel width in the number of pixels for each segment.

4.5.4 Retinal Morphology

In addition to the automated reading of images a manual review of the digital retinal images was carried out in order to record any changes seen within the retinal field, including retinal vessel characteristics. This is important since the QUARTZ program removes all bifurcation and cross-over points of vessels which are known to have clinical utility, such as arteriovenous nipping in individuals with hypertension. All retinal images of participants with a diagnosis of PMR and or GCA were reviewed in addition to matched control cases for those individuals with incident diagnoses of PMR or GCA (i.e. occurring after their retinal photograph was taken). Characteristics recorded were based on a modification of the National Health and Nutrition Examination Survey (NHANES) programme to capture vascular lesions such as focal narrowing and arteriovenous nipping (See Appendix 2 for scoring sheet).

4.5.5 Validation of retinal findings

All retinal images of the participants were analysed at Moorfields eye hospital with the author reviewing all the cases and control images. In addition an independent review of all the images was undertaken by a retinal screening programme technician. Where any cases of disagreement occurred a third, senior technician reviewed the images who had the final say on any morphological features present.

4.6.0 Construction of the PMR cohort to monitor for polyarthritis development

The European Prospective Investigation in Cancer and Nutrition Norfolk (EPIC-Norfolk) is a prospective cohort study of 24,068 participants recruited from 35 general practice sites in the years 1993 to 1997 (211). Of secondary care outpatient attendances for EPIC-Norfolk participants, 94.9% are at a single hospital in the region (Norfolk and Norwich University Hospital). The study period was restricted to the interval between 1st February 2002 and 31st January 2015 when laboratory data were available on all subjects.

4.6.1 Identification and definition of incident polyarthritis

All cases of PMR identified within the EPIC-Norfolk cohort underwent hospital records review. To satisfy a diagnosis of PMR, patients were

required to be older than 40 years and to have received at least two prescriptions for oral glucocorticoids within six months of the index date of diagnosis. This approach has been validated in the Clinical Practice Research Datalink (CPRD) (120). Case assignment for PMR was carried out independently by two rheumatologists (MY, RW). Potential cases were excluded from the analysis if the diagnosis in the case record was refuted, or changed within the first six months to an alternative diagnosis other than inflammatory polyarthritis (IP). IP was defined on the basis of rheumatology records which documenting wrist and/or peripheral joint synovitis with a decision to start DMARD therapy (most commonly methotrexate). Case assignment for IP was carried out independently by two rheumatologists (MY, JK). Participants with a diagnosis of IP prior to PMR were excluded from subsequent analysis.

4.7.0 OVERVIEW OF THE ANALYTICAL APPROACHES

The datasets analysed as part of this thesis comprise both cross-sectional and cohort studies, which allows for and dictates the form of analysis possible. From the observed data, inferences are used to make predictions of the probability or chance for the outcome following exposure to the risk factor for future or unobserved individuals. Therefore any analysis of a sub-section of a population (commonly referred to as the sample) is assumed to be representative of the total population from which it is drawn. Controls which are unrepresentative of the population

from which cases derive can introduce bias with uncertainty in the resulting estimate.

The initial Results Chapters deal with the descriptive epidemiology for PMR and GCA namely their prevalence and incidence and subsequently the absolute and relative risks for visual impairment. The later Results chapters describe the factors associated with both disease onset and progression. Since the three datasets comprise cross-sectional and cohort data, the analytical approaches differ and are set out below.

4.7.1 Cross-sectional data

By definition, cross-sectional studies capture single-time point data. Cases, defined as having the outcome of interest, are compared to controls, those without the outcome. Exposure to certain risk factors is compared between the two groups to derive an inference regarding that particular exposure and its association to the outcome. Since the date of the outcome of interest is not calculated with duration of exposure, rates cannot be estimated. Cross-sectional or more commonly case-control studies can be analysed to estimate odds or risk (220).

Case-control studies are considered an ideal design for studying rare diseases, where a cohort study would be required to be very large and have a long duration of follow-up making it costly and logistically difficult. The main limitations of case-control studies are difficulty in finding

representative control groups and that rates of disease cannot be calculated. Other problems include recall and reverse causation bias.

However, this study design is used in analysing the GCANS and DCVAS data since they are cross-sectional studies. The minimum period prevalence for PMR and GCA can be calculated from GCANS and the prevalence of blindness in patients with GCA recruited to DCVAS. In addition since EPIC-Eye is a case-control study nested within the cohort study of EPIC-Norfolk, the relative and absolute risks for visual impairment can be calculated.

4.7.2 Cohort data

Cohort data comprise a group of individuals of whom none have the outcome of interest at the start of the observation period. The cohort is then monitored for a period of time, at the end of which those with the outcome are compared to those without and comparisons are made in the exposures between the two groups in order to draw inference about their associations. The data have the duration of time an individual is potentially exposed to the risk factor, so rates of disease and risks can be calculated unlike case-control studies. Cohort studies have the further advantage of being able to be analysed to calculate both absolute and relative risks for an exposure for a given population (220). Analytical methods need to take account of longitudinal nature of exposure and censorship. These methods apply to the EPIC-Norfolk data. Due to the

longitudinal set-up the incidence of PMR and GCA can be investigated and is reported for the EPIC-Norfolk cohort.

4.8.0 ESTIMATES OF FACTORS ASSOCIATED WITH ONSET AND PROGRESSION OF DISEASE

In addition to describing the descriptive epidemiology, it is possible to measure both rates and risks for factors associated with disease onset and progression. The data sets allow studies of both case-control design and survival methods for modelling of risk factors.

4.8.1 Case-control studies

Case-control studies can be used to investigate factor associated with disease outcome. In this thesis, factors associated with disease onset and progression will be assessed using logistic regression with risk estimated using odds ratios. These include cardiovascular risk factors and medication associated with diagnosis of PMR and GCA, and factors associated with blindness in GCA.

4.8.2 Survival analysis

Risk can be estimated from cumulative incidence and incidence density. However, incidence density has advantages over cumulative incidence since, the latter allows for losses to follow-up, competing risks and differential follow-up time for participants. This is particularly important

for analysis of the EPIC-Norfolk cohort which had a relatively long enrolment period and long-duration of follow up. In addition expression of incidence density estimates for disease outcome has advantages in being comparable to other studies which have also produced estimates using this method.

Generally the longer individuals are observed, the more chance they will have of developing the outcome of interest. Therefore it would be misleading to compare one study with five years of follow-up for the risk for a particular exposure to another that had ten years of follow-up. In addition, once the outcome of interest has developed, that particular individual can no longer be at risk and it cannot be known when that outcome developed (right censored). For this reason risks cannot take account of time-varying exposures, so called time-dependent variables (220).

The cohort data from the EPIC-Norfolk study allows for calculation of estimates of disease incidence rate. Due to the dynamic nature of the cohort (i.e. long enrolment phase and long duration of follow-up), incidence density is the most appropriate form for expressing new disease occurrence. However, there are several steps required in the process of building a model which are described below.

4.9.0 MODELLING ASSOCIATIONS

Several plausible biological risk factors exist for both disease onset and progression in PMR and GCA. Previously published estimates are hampered by small sample size, unrepresentative control groups, lack of community-based estimates, and recall bias. Several methods of modelling are available to test associations between putative risk factors and outcomes of interest. In the datasets of case-control design used in this project, logistic regression is suitable for the purpose of modelling associations with the outcomes available. The computer program STATA estimates the parameters in a multivariate logistic regression model using maximum likelihood. The output displays p values based on the Wald test.

Stepwise logistic regression is used with likelihood ratio tests to examine whether the model steps are significantly different in their output. However, often data for variables is missing and therefore it is not possible to perform a likelihood ratio test because the more complicated model needs to be nested within the simpler version.

Analytical methods using survival analysis are more complicated. Depending on the methods used there are several assumptions to be aware. Incidence density is the most appropriate measure of disease occurrence in EPIC-Norfolk, this will be used for analytical modelling purposes. Since age and sex are likely to be strong confounders in the

development of both PMR and GCA, the relationship between these two factors will need to be investigated. Using Lexis expansion, age bands are created so that each resulting record contains the follow-up on one subject through one time band allowing for adjustment due to confounding by age. Participants are censored (no longer contribute at risk time) when they develop either disease of interest or die. The rate ratios for disease onset can be calculated to test the assumption of whether the effect of sex differs across age bands. If it does not then more complicated methods of survival analysis can be explored including Cox regression as there is no violation of proportionality.

In addition, the rate of co-morbidity can be studied, e.g. those who develop polyarthritis (IP) following a diagnosis of PMR. Since PMR and GCA affect older people, it is likely that there will be associated expected mortality. For these reasons survival analysis will need to take account of deaths that occur in the cohort. Kaplan Meier is the most commonly used method, producing a survival curve often called the survivor function but is non-parametric and is unable to be used with more than one predictor variable. Cox regression, or more precisely Cox Proportional Hazards model, allows for multiple predictors in the model and produces a hazard function, its main assumption being that the proportional hazards stay constant over time (221).

The analytical plan will therefore comprise: first studying the effect of age and sex, using Lexis expansion, if there are no statistical differences for

the effect of sex across the age bands then Cox regression will be used with finally competing risk of death due to the elderly nature of the cohort.

As with any observed data there is also the potential for unobserved confounding for which no model can account.

4.9.1 Approaches to confounding

There is no statistical test for confounding, which occurs when a variable is associated both with the risk factor and the outcome but is not a causal factor. Confounding can be dealt with either by use of modelling or stratification. Stratification can be used if there are enough individuals or observations in each strata and it does not require the investigator to know assumptions about the distribution of the confounder within each stratum or the relationship between each confounder variable. When there are few observations to make strata cut-points feasible, modelling has the advantage over stratification. However to prevent spurious conclusions, the distribution and relationship of the confounder variable have to be considered in the model for example assessing the effect of age over age strata.

4.9.2 Bias

Bias can be introduced anywhere in the study process, from the design and set-up to case ascertainment and validation, to the way the results

are analysed. Studying associations between possible risk factors and disease outcomes are particularly difficult in older aged populations mainly due to confounding by indication.

4.9.3 Summary of the analytical approaches

Of the datasets presented in this thesis, each have their advantages and disadvantages in respect of the analysis possible. Chapter six details the risk of morbidity associated with PMR and GCA, with the EPIC dataset ideally suited to analyse such associations. DCVAS contains only cases of vasculitis or comparator conditions, where vasculitis was or could be suspected but ultimately was not confirmed by the treating physician and so cannot be used to make estimates of incidence or prevalence of PMR or GCA. For the risk of inflammatory polyarthritis following a diagnosis of PMR, the standard Cox-proportional hazard model was extended to include a competing risk for death using the Fine-Gray method (222). A summary of the different data sets and statistical approaches is displayed in the Table 4.2 below.

Table 4.2 Summary of statistical methods

Estimate	Data source	Statistical method
Prevalence of PMR and GCA	GCANS	Minimum cumulative prevalence (period prevalence)
	EPIC-Norfolk	Minimum cumulative prevalence (period prevalence)
Incidence of PMR and GCA	EPIC-Norfolk	Incidence rate per 100,000 person years (incidence density)
Visual impairment in cases with PMR and GCA	EPIC-Norfolk Eye study	Absolute risk and logistic regression
Blindness in GCA	DCVAS	Absolute risk
Risk factors for disease onset		
Age, sex genetic and traditional cardiovascular risk factors	EPIC-Norfolk	Lexis expansion for age with rate ratios
		Logistic regression for smoking and other traditional cardiovascular factors
		Logistic regression for previously identified genetic loci
		Cox-proportional hazard ratios for traditional cardiovascular risk factors
		Cox-proportional hazards with Fine-Gray extension for traditional cardiovascular risk factors
		Logistic regression for common medication at baseline, including anti-hypertensives and lipid lowering medication
Risk factors for progression		
Risk factors for blindness associated with GCA	DCVAS	Odds ratios for risk factors including previous medical conditions including cardiovascular disease
Risk factors for inflammatory polyarthritis associated with PMR	EPIC-Norfolk	Cox-proportional hazards with Fine-Gray extension for baseline clinical features at time of PMR diagnosis
Retinal morphology including vasculometric measures	EPIC-Norfolk Eye study	Linear regression modelling to compare differences in mean widths for retinal vessel venules and arterioles between controls and cases of PMR and GCA
		Retinal morphology characteristics in case-control (matched 1:3) with test on counts using Chi^2 or Fisher's exact tests when appropriate

CHAPTER 5 ESTIMATES OF PREVALENCE AND INCIDENCE

5.0 SUMMARY

The prevalence and incidence of PMR and GCA and their complications are described using information from the Norfolk population using GCANS and EPIC-Norfolk datasets.

The GCANS study was designed to provide community-based prevalence estimates. Part of the study surveyed the practice population to estimate the frequency of symptoms commonly associated with PMR and GCA to provide an indication of the number in the community with undiagnosed disease. All confirmed diagnoses of GCA fulfilled the 1990 American College of Rheumatology (ACR) classification criteria. Of confirmed PMR diagnoses, 67-89% fulfilled classification criteria, depending on the criteria used. In summary, the GPs' diagnosis of PMR/GCA was sensitive although not all diagnoses fulfilled classification criteria. In addition a minority of patients had their diagnoses switched subsequently to an alternative diagnosis, suggesting that GP diagnoses for PMR and GCA may lack specificity (this is discussed further in the subsequent sub-headings on GCANS 5.1.0).

For EPIC-Norfolk, amongst the 25,639 participants, aged 40-79 years, recruited between the years 1993-1997 there were 404 diagnoses of PMR and 123 diagnoses of GCA to the end of the follow-up (31st March 2015).

After accounting for those individuals who died the cumulative prevalence estimates were calculated for those aged over 50 years old. Similar to GCANS, not all diagnoses met the current classification sets, with 61.7% of GCA cases meeting the 1990 ACR criteria for GCA and 70.4% of PMR cases meeting the current EULAR/ACR criteria (this is discussed further in the following sub-headings on EPIC-Norfolk 5.2.0).

5.1.0 PREVALENCE OF PMR AND GCA IN NORFOLK – GCANS

The prevalence of PMR and GCA was calculated from a single GP practice in Norfolk by the GCANS study (Giant cell arteritis in Norfolk study). The calculated prevalence was based on a minimum cumulative estimate for all diagnoses of PMR and GCA. This study used review of GP practice records supplemented by a postal survey (Figure 4.1 shows a flowchart for the sampling method). The cumulative prevalence took account of all registered individuals on the GP register irrespective of whether they returned the postal questionnaire. As a result the cumulative prevalence estimate will represent a minimum estimate and not be upwardly biased.

5.1.1 Database search

A total of 6,159 patients registered with the practice were aged 50 years and older, of whom 117 had a diagnosis of PMR and 22 had a diagnosis of GCA in their care record.

5.1.2 Survey

A total of 5,159 patients registered with the practice were aged ≥55 years with a median age of 62.5 years, of whom 2,706 (52.5%) were female. After applying exclusion criteria, the postal survey was sent to all eligible individuals aged 55 years or older. The exclusion criteria comprised those with terminal illness, dementia, nursing home residents or those individuals who had previously informed the practice they did not wish to take part in research.

Questionnaires were sent to 4,728 eligible patients registered with the practice to discover any missed diagnoses of PMR and GCA not recorded in the GP register. Of the 2,277 (48% response rate) returned questionnaires, 97.2% had complete data. The median age of respondents was 70 years and 52% were female. The age and sex distribution of the non-responders was similar to that of the responders (Table 5. 1).

5.1.3 Clinical review of questionnaire respondents

A total of 15 individuals reported a diagnosis of GCA, nine of whom were confirmed by the practice record and fulfilled the 1990 ACR classification criteria. In all nine cases the diagnoses were confirmed following referral to secondary care specialists including rheumatologists, ophthalmologists, geriatricians and neurologists. These subjects were not invited for further clinical review.

Among the remaining 2,268 respondents who did not have a GP-recorded diagnosis of PMR or GCA, 31 reported the triad of visual disturbance, scalp tenderness and symptoms suggestive of jaw claudication. All these were contacted and following clinical review, none were thought to have GCA. At least one symptom was reported in 1,007 respondents. Of these, a sample of 93 were reviewed and 25 had reported symptoms suggestive of PMR without key features of GCA: namely, lack of headache, jaw claudication, visual disturbance or scalp tenderness. After clinical review none were thought to have undiagnosed PMR nor GCA. All those invited attended for assessment. Table 5.1 lists the clinical characteristics of the survey responders.

Table 5.1. Characteristics of survey responders

Characteristics	Total Population	Survey Pool	Survey Responders	PMR Self-reported	PMR Confirmed by GP	GCA Self-reported	GCA Confirmed by GP
Number ≥55 years	5,159	4,728	2,277	83	73	15	9
Median age, years	62.5	68.0	70.0	75.6	75.8	72.1	73.9
Female (%)	52.2	53.6	52.0	70.0	67.4	78.6	71.5
Clinical features reported on questionnaire							
Headache (%)			4.7	8.4	9.5	31.3	55.6
Jaw Pain (%)			7.5	20.5	19.2	31.3	44.4
Visual Disturbance (%)			19.8	22.9	24.7	37.5	44.4
Scalp Tenderness (%)			7.8	15.7	6.2	56.3	88.9
Shoulder Pain (%)			24.9	67.5	67.1	50	77.8
Myalgia (%)			18.8	68.7	67.1	43.8	55.6
Unexplained Weight loss (%)			4.2	12.1	11.0	31.3	55.6
Migraine with aura (%)			15.0	14.6	16.7	18.8	11.1
No Symptoms (%)			55.8	20.5	21.9	18.8	0.0

Of the 83 who reported a diagnosis of PMR on the questionnaire, 73 cases were confirmed to have the condition by the practice. Practice records confirmed the diagnoses of the two respondents with both PMR and GCA.

All participants reporting diagnoses of either GCA (n=6) or PMR (n=10) but without confirmation on the GP record were contacted by telephone. The discrepancy was found to be either due to participants misreading arteritis for arthritis on the questionnaire, or to the diagnoses being refuted by the GP later and withdrawn.

5.1.4 Case classification

Based on the information included in the GP record, of the 21 cases identified with GCA, a total of 13 fulfilled the 1990 ACR classification criteria set, with a median age of 70 years at diagnosis and a mean ESR of 74 mm/hr. The remaining eight failed to fulfil classification criteria based on their inflammatory marker results and the absence of typical histological findings on temporal artery biopsy; of these, six had changed GP practice and had insufficient diagnostic information on their records.

The five most commonly-used classification criteria sets for PMR used in the previous published estimates all rely on the combination of typical clinical features, age and elevated inflammatory markers but the cut-points for these vary (Table 2.2).

Of the 117 cases identified in the GP records with PMR, 73 (71%) were female and a median age was 70 years. Inflammatory marker results, prior to steroid initiation, were available for 100 patients (96 with ESR; mean 45 mm/hr; 33 with CRP, mean 50 mg/dL; and 29 had both). Of these 100 individuals, the proportion of those satisfying the different criteria sets are: 47% (Bird), 62% (Chuang), 62% (Healey), 62% (Doran), and 79% (Jones and Hazleman). The majority of PMR cases (71%) were managed exclusively in primary care with no further information available for more detailed classification.

5.1.5 Prevalence estimates for PMR and GCA

Of those cases which could be identified reliably through GP record review (namely those who had treatment with glucocorticoids *and in whom* the diagnosis was not later refuted), the minimum cumulative prevalence estimate for GP-diagnosed cases of GCA was 0.41% (95% CI 0.23%, 0.58%) and for PMR was 2.27% (95% CI 1.86%, 2.67%) Table 5.2 shows age and sex specific cumulative prevalence for both conditions.

Table 5.2 Cumulative prevalence estimate by sex and age bands based on GP records

Age, years	N	Female	Male	PMR		Female		Male		GCA		Female		Male	
				N	Pr (95%CI)	N	Pr (95%CI)	N	Pr (95%CI)	N	Pr (95%CI)	N	Pr (95%CI)	N	Pr (95%CI)
55-59	978	500	478	1	0.10 (0.00, 0.30)	1	0.20 (0.00, 0.59)	0		1	0.10 (0.00, 0.30)	0		1	0.21 (0.00, 0.62)
60-69	1902	989	913	20	1.05 (0.59, 1.51)	15	1.52 (0.76, 2.28)	5	0.55 (0.07, 1.03)	3	0.16 (0.00, 0.34)	3	0.30 (0.00, 0.65)	0	
70-79	1412	700	712	49	3.47 (2.52, 4.43)	33	4.71 (3.14, 6.28)	16	2.25 (1.16, 3.33)	6	0.43 (0.09, 0.76)	4	0.57 (0.01, 1.13)	2	0.28 (0.00, 0.67)
80-89	695	395	300	40	5.76 (4.02, 7.49)	20	5.06 (2.90, 7.22)	20	6.67 (3.84, 9.49)	9	1.30 (0.45, 2.14)	5	1.27 (0.16, 2.37)	4	1.33 (0.04, 2.63)
90-100	166	116	50	7	4.22 (1.16, 7.27)	5	4.31 (0.62, 8.01)	2	4.00 (0.00, 9.43)	2	1.72 (0.00, 4.09)	2	1.72 (0.00, 4.09)	0	
100+	6	6	0	0		N/A		N/A		0		N/A		N/A	
Total	5159	2706	2453	117	2.27 (1.86, 2.67)	74	2.74 (2.12, 3.35)	43	1.75 (1.23, 2.27)	21	0.41% (0.23, 0.58)	14	0.52 (0.25, 0.79)	7	0.29 (0.07, 0.50)

***N: total number of people registered with the practice. Pr (95% CI): cumulative prevalence with 95% confidence interval based on the Poisson distribution**

For those to whom it was possible to apply the 1990 ACR classification criteria retrospectively, cumulative prevalence of GCA was 0.25% (95% CI 0.11 to 0.39). Applying the various classification criteria retrospectively to GP-diagnosed cases of PMR (Table 5.3) gave the following cumulative prevalence estimates: Bird criteria 0.91% (95% CI 0.65 to 1.17); Chuang, Healey and Doran criteria 1.20% (95% CI 0.90 to 1.50); and Jones and Hazleman criteria 1.53% (95% CI 1.20 to 1.87).

Table 5.3 Cumulative prevalence estimates for cases which satisfy classification criteria applied to GP record data.

Criteria set	All		Female		Male	
	N	Pr (95%CI)	N	Pr (95%CI)	N	Pr (95%CI)
GCA (21 cases reported in GP records)						
Hunder	13	0.25 (0.11, 0.39)	9	0.33 (0.12, 0.55)	4	0.16 (0.00, 0.32)
PMR (117 cases reported in GP records)						
Bird	47	0.91 (0.65, 1.17)	28	1.04 (0.65, 1.42)	19	0.78 (0.43, 1.12)
Healey; Chuang; Doran	62	1.20 (0.90, 1.50)	39	1.44 (0.99, 1.89)	23	0.94 (0.56, 1.32)
Jones and Hazleman	79	1.53 (1.20, 1.87)	49	1.81 (1.31, 2.31)	30	1.22 (0.79, 1.66)

N: total number of people identified in the practice. Pr (95% CI): cumulative prevalence with 95% confidence interval calculated using the Poisson distribution based on a total population of 5,159 (2,706 female, 2,453 male). Inflammatory markers were available in 100 out of 117 GP record cases (of which 96 had ESR and 33 CRP with overlap of 29 cases with both CRP and ESR results at time of diagnosis).

5.1.6 Comments

These are the first community-based estimates for the prevalence of PMR and GCA in the UK for over 30 years and from these data, it appears unlikely that there are cases of PMR and GCA in the community unknown to their General Practitioner.

There is no validated questionnaire for the purposes of classification or diagnosis of PMR or GCA. An instrument was required that was sensitive to the entire range of symptoms which can be associated with either PMR or GCA. Every effort was made to enrich the available clinical data using direct record, questionnaire sampling and clinical review. Of the 5,159 potential participants selected based on age, after applying exclusion criteria 4,728 were contacted via the postal survey, a 48% response rate was received. It is encouraging that 55.8% of responders returned the questionnaire had no symptoms, perhaps indicating that the majority with symptoms returned the questionnaire.

Around half of the cases diagnosed with PMR or GCA fulfil appropriate classification sets, which may be a problematic when comparing community-based and hospital-based cohorts due to selection bias.

5.2.0 EPIC-NORFOLK

The GCANS study discussed above indicated the need for more detailed verification of cases. The next phase required verification of the cases

having occurred within the EPIC-Norfolk cohort. Electronic and paper records were reviewed to extract clinical information to confirm diagnoses of PMR and GCA and to allow retrospective application of the classification criteria sets for the two diseases.

Having arranged the necessary collaboration agreements with EPIC-Norfolk potential cases of PMR and GCA within the cohort were identified.

5.2.1 Baseline characteristics of the EPIC-Norfolk cohort

The baseline characteristics of the EPIC-Norfolk cohort are shown in Table 5.4 and Table 5.5 shows the clinical features of the cases. The cases of PMR and GCA are first defined as those over the age of 50 as set-out above in section 4.3.3 and 4.3.4. Subsequently the cases were defined by those meeting the current classification criteria sets for PMR and GCA respectively.

Table 5.4 Baseline characteristics of the EPIC-Norfolk cohort

Characteristics (Cases - age over 50)	PMR50 (n = 395)	GCA50 (n = 118)	Control (n = 25,147)
Age at baseline*	64.5	64.6	58.9
Female, n (%)	294 (74.4)	88 (74.6)	13,670 (54.4)
Never smoker, n (%)	197 (49.9)	47 (39.8)	11,443 (45.5)
High Blood pressure†, n (%)	78 (19.8)	23 (19.5)	3,570 (14.2)
Systolic BP (mm/Hg) (SD)	140 (20)	135 (16)	135 (18)
Diastolic BP (mm/Hg) (SD)	84 (12)	82 (11)	83 (11)
Diabetes†, n (%)	7 (1.8)	2 (1.7)	581 (2.3)
BMI (kg/m^2) (SD)	26.7 (3.9)	26.0 (3.7)	26.4 (3.9)
Triglycerides (mmol/L)*	1.6	1.6	1.5
HDL (mmol/L) (SD)	1.49 (0.42)	1.47 (0.42)	1.42 (0.43)
LDL (mmol/L) (SD)	4.30 (1.16)	4.21 (1.09)	3.96 (1.03)
Alcohol (units/week)*	2.5	2.5	3.5
N-6 Polyunsaturated fatty acids (g)*	9.9	9.1	9.9
N-3 Polyunsaturated fatty acids (g)	1.6	1.6	1.6
Loss of adult teeth, n (%)	360 (91.1)	109 (92.4)	21,347 (84.9)
Parity four or more children, n (%)	41 (14.0)	13 (14.8)	1,391 (10.2)
Characteristic (Cases - meeting classification sets)	**PMR (n = 272)**	**GCA (n = 76)**	**Control (n = 25,312)**
Age at baseline*	64.6	64.6	60
Female, n (%)	204 (75.0)	57 (75.0)	13,791 (54.5)
Never smoker, n (%)	139 (51.7)	30 (41.1)	11,518 (45.9)
High Blood pressure†, n (%)	52 (19.2)	19 (25.0)	3,600 (14.3)
Systolic BP (mm/Hg) (SD)	140 (20)	136 (17)	135 (18)
Diastolic BP (mm/Hg) (SD)	84 (12)	82 (11)	83 (11)
Diabetes†, n (%)	5 (1.8%)	2 (2.6%)	583 (2.3%)
BMI (kg/m^2) (SD)	26.3 (3.6)	25.7 (3.5)	26.4 (3.9)
Triglycerides (mmol/L)*	1.6	1.6	1.5
HDL (mmol/L) (SD)	1.48 (0.40)	1.47 (0.38)	1.42 (0.43)
LDL (mmol/L) (SD)	4.30 (1.13)	4.23 (0.96)	3.96 (1.04)
Alcohol (units/week)*	2.5	3	3.5
N-6 Polyunsaturated fatty acids (g)*	9.7	8.8	9.9
N-3 Polyunsaturated fatty acids (g)	1.5	1.5	1.5
Loss of adult teeth, n (%)	251 (93.7)	70 (93.3)	21,495 (88.0)
Parity four or more children, n (%)	29 (14.2)	7 (12.3)	1,409 (10.2)

*medians, otherwise arithmetic means and standard deviations are presented (SD), †Self-reported at baseline questionnaire.

Table 5.5 Clinical features of PMR and GCA cases

Clinical Features	PMR50	PMR EULAR/ACR	GCA50	GCA ACR
Age at Diagnosis*	73.6 (8.6)	73.5 (8.6)	74.1 (8.5)	74.9 (8.5)
Female, n (%)	294 (74.4)	204 (75.0)	88 (74.6)	57 (75.0)
Diagnosed exclusively by GP, n (%)	254 (65.0)	182 (67.4)	14 (12.1)	4 (5.4)
ESR at Diagnosis (mm/hr)	56 (30)	57 (29)	73 (34)	89 (24)
CRP at Diagnosis* (mg/L)	30	28	52	79

*medians, otherwise arithmetic means and standard deviations are presented (SD)

5.2.2 Prevalence of PMR and GCA from EPIC-Norfolk

Prevalence estimates for PMR and GCA were calculated for the EPIC-Norfolk participants. This included all cases which developed over the observation period and therefore is a point prevalence estimate.

The cohort was monitored until the 31st March 2015. During this time, 21 individuals had not reached the age of 50. To account for deaths, those who had died were also excluded from the analysis for the purposes of generating cumulative point prevalence estimates.

PMR

There were 404 incident diagnoses of PMR and restricting to those older than 50 years resulted in 395 cases. Due to deaths in the cohort, 295 cases who had a diagnosis of PMR were still alive at the end of the study period. This resulted in a point prevalence of 1.62% (95% CI 1.44%, 1.80%) on the 31st March 2015. Restricting to cases which fulfilled the

EULAR/ACR criteria set resulted in 207 cases of PMR with a corresponding prevalence estimate for PMR of 1.14% (95% CI 0.98%, 1.29%).

GCA

There were 123 patients with a diagnosis of GCA of whom 118 were aged over 50 years at time of diagnosis. Due to the deaths in the cohort, 85 cases with a diagnosis of GCA and were still alive at the end of the study period. This resulted in a point prevalence estimate for GCA of 0.47% (95% CI 0.37%, 0.57%) on the 31st March 2015. Restricting to cases which fulfilled the ACR criteria set resulted in 76 cases of GCA with a corresponding prevalence estimate of 0.29% (95% CI 0.21%, 0.36%).

5.2.3 Incidence of PMR and GCA from EPIC-Norfolk

Incidence for PMR and GCA were calculated for the EPIC-Norfolk participants. During the follow-up period to 31st March 2015 of the cohort of 25,660 recruited at baseline, there were 398 incident cases of PMR and 123 cases of GCA diagnosed. There were 24 participants who had missing date-of-entry at the baseline time point. Excluding cases diagnosed under the age of 50 years resulted in 395 cases of PMR and 118 cases of GCA.

The cohort of 25,636 participants had a total follow-up time of 440,236.9 person years (pyrs) at risk. This was used as the denominator for the purposes of calculating incidence density.

PMR

The incidence of PMR for those aged 50 or older was 89.7 (95% CI 81.3, 99.0) per 100,000 pyrs. Restricting the analysis to those 272 cases of PMR fulfilling the EULAR/ACR classification criteria set resulted in an incidence rate of 61.8 (95% CI 54.9, 69.6) per 100,000 pyrs at risk.

GCA

The incidence of GCA for those aged 50 or older was 26.8 (95% CI 22.4, 32.1) per 100,000 pyrs. Restricting the analysis to those 76 cases of GCA fulfilling the ACR classification criteria set resulted in an incidence rate of 17.3 (95% CI 13.8, 21.6) per 100,000 pyrs at risk.

5.2.4 Comments

This large, extensively phenotyped cohort has been used to calculate incidence rates for PMR and GCA which apply current classification criteria. The EPIC-Norfolk cohort is representative of the wider community in Norfolk but being largely Caucasian, the wider generalisability of the findings to other parts of the UK and world is limited. It is encouraging that the median age of diagnosis and sex distribution is in line with previously published data. The estimated incidence rates are similar to other UK-based estimates, which in turn are comparable with estimates of disease incidence from the United States and Northern European countries and in turn the prevalence estimate

from the USA (see Tables 2.3 and 2.4). The wider significance of these findings is discussed in Section 5.4.

5.3.0 ESTIMATES OF OCULAR MORBIDITY

The EPIC-Norfolk and DCVAS studies are ideally suited to measuring ocular morbidity due to comprehensive visual assessment, and allowing for accurate contemporary estimates of ocular morbidity to be produced for the first time. Details of the assessments is described earlier in Sections 4.4.4 and 4.5.1.

5.3.1 EPIC-Eye Study

A total of 8,623 participants aged 48-92 years attending the Eye Study (nested within EPIC-Norfolk) underwent assessment of visual acuity, measured using a logarithm of the minimum angle of resolution chart (LogMAR chart), which replaces the older Snelling Chart for measuring visual acuity. A LogMAR value of 0.0 corresponds with a Snellen equivalent of 6/6. The World Health Organisation (WHO) used LogMAR values to standardised definitions for visual impairment, low vision and blindness with the higher the LogMar value the worse the vision (see Section 4.5.1).

5.3.2 Visual acuity thresholds in EPIC-Eye

Data on visual acuity were available for 8,052 participants, comprising 4,464 women (55.4%) of the cohort. The mean age at the third health

check was 68.8 years (SD 8.1). See Table 5.6 for visual acuity thresholds by those with and without GCA and or PMR.

Table 5.6 Visual acuity thresholds in EPIC-Eye

Visual thresholds	PMR (n = 132)		GCA (n = 42)		Controls (n = 7,938)	
	Eyes	Participants	Eyes	Participants	Eyes	Participants
Visual impairment	Left 7 (5.7%) Right 12 (9.8%)	2 (1.6%)	Left 6 (14.3%) Right 2 (4.8%)	0	Left 284 (3.6%) Right 272 (3.4%)	46 (0.6%)
Low vision	Left 5 (4.1%) Right 9 (7.3%)	1 (0.8%)	Left 6 (14.3%) Right 2 (4.8%)	0	Left 252 (3.2%) Right 236 (3.0%)	40 (0.5%)
Blindness	Left 2 (1.6%) Right 3 (2.4%)	1 (0.8%)	Left 0 Right 0	0	Left 25 (0.3%) Right 27 (0.3%)	2 (0.03%)

The above counts include all those with a diagnosis of GCA or PMR irrespective of their health check three date. Number of eyes affected are reported and secondly, number of participants in line with WHO definitions for visual impairment, low vision and blindness. WHO definitions refer to vision in the better eye to define level of visual impairment – it is therefore possible to be blind in one eye and yet considered to have no visual impairment (See Section 4.5.1 for details).

Sensitivity analysis – visual acuity

The resultant age- and sex-adjusted odds ratios (ORs) for the different grades of visual impairment affecting either eye were as followings: visual impairment: GCA OR = 4.10 (95% CI 1.44, 11.72 p = 0.008) and PMR OR = 1.43 (95% CI 0.74, 2.76 p = 0.290); low vision, GCA OR = 4.75 (95% CI 1.67, 13.54 p = 0.004) and PMR OR = 1.17 (95% CI 0.55, 2.48 p = 0.681); and blindness; no cases in the GCA group, PMR OR = 3.85 (95% CI 1.14, 13.04 p = 0.03). This analysis included all participants irrespective of the timing of their diagnosis of PMR or GCA. Therefore, some participants had undergone their visual assessment prior to their diagnosis of PMR or GCA and will result in a downward bias in the estimate for visual impairment.

Of the cases occurring before their third health check, ten met the 1990 ACR criteria for GCA and 59 met the EULAR/ACR criteria for PMR. If only those cases meeting the classification sets are used to define GCA and PMR, the resultant odds ratios are as follows: visual impairment, GCA OR = 5.21 (95% CI 1.31, 20.77 p = 0.019) and PMR OR = 1.48 (95% CI 0.69, 3.18 p = 0.312); low vision; GCA OR = 6.03 (95% CI 1.52, 23.91 p = 0.011) and PMR OR = 1.26 (95% CI 0.53, 2.98 p = 0.600); and blindness, no cases in the GCA group, PMR OR = 3.38 (95% CI 0.78, 14.67 p = 0.105).

The results reveal that participants with GCA had worse vision than controls, and that participants' vision does not seem to be affected by a diagnosis of PMR.

5.3.3 DCVAS ocular morbidity

DCVAS uses the vasculitis damage index (VDI) to record damage associated with a diagnosis of vasculitis. This item was completed retrospectively at the six month time point, following the diagnosis of vasculitis.

5.3.4 Cases of GCA and blindness in DCVAS

Of the 715 patients recruited into DCVAS by December 30th 2014 with complete data: 433 were considered to have GCA with ≥75% diagnostic certainty at six months; 404 fulfilled the 1990 ACR criteria for GCA; and 235 had a positive temporal artery biopsy. The patients were mainly (95.6%) Caucasians from Europe or North America (baseline characteristics - Table 5.7). Six months after diagnosis, 34 (7.9%) patients had at least monocular blindness, of whom 3 (0.7%) had binocular blindness (with no statistical significant difference in the rate of blindness between men and women).

Table 5.7 Clinical Features at baseline of patients with giant cell arteritis in the DCVAS study

Clinical Features	Physician Diagnosis of GCA at 6 months (>75% certainty) n=433		
	Blind at six months (n=34)	Not blind at six months (n=399)	*p*-value*
Age at diagnosis (median, years)	74.9	73.0	0.073
Male (%)	12 (35.3)	133 (33.3)	0.816
New-onset headache	23 (67.7)	282 (70.7)	0.710
Any visual symptom (%)	32 (94.1)	154 (38.6)	0.000
Jaw claudication (%)	13 (38.2)	163 (40.9)	0.766
Tongue claudication (%)	3 (8.8)	16 (4.0)	0.188
Morning stiffness shoulders arms (%)	7 (20.6)	87 (21.8)	0.869
Morning stiffness hips/thighs (%)	5 (14.7)	69 (17.3)	0.700
Myalgia (%)	5 (14.7)	109 (27.3)	0.109
Fever (%)	3 (8.8)	68 (17.0)	0.214
Fatigue (%)	13 (38.2)	164 (41.1)	0.744
Weight loss (%)	12 (35.3)	138 (34.6)	0.934

**p*-value of difference between those who were subsequently declared blind in at least one eye versus those who were not; all calculated using the chi squared test except for median age at diagnosis, ESR and CRP which was tested by the Mann-Whitney test.

Of the patients who had blindness recorded at six months, 31 (22 women and 12 men) had presented with symptoms of sudden visual loss, with only two patients with no visual disturbance (including amaurosis fugax, visual loss, blurred vision or diplopia) at baseline being declared blind at six months. The visual manifestations of disease for all patients with GCA at presentation included: blurred vision in 98 (22.6%), sudden visual loss in 70 (16.2%), diplopia in 51 (11.8%), amaurosis fugax in 33 (7.6%), and red eyes in nine (2.1%). As expected, blindness at six months

occurred more frequently in those who presented with visual symptoms. Of those with sudden visual loss at presentation, 44.3% (31/70) were blind at six months as assessed using the VDI; of those with no recorded visual loss at presentation, 0.8% (3/363) were recorded as being blind at the six month review.

5.3.5 Comments

While the EPIC-Norfolk eye study sample of 8,623 participants is relatively small, it is strengthened by the detailed visual acuity assessment. To date, studies of sight-loss in GCA have been mainly of case-series design with lack of ability to estimate relative risks. In addition the author is unaware of any study which documents visual performance in individuals diagnosed with PMR.

Although there was no formal ophthalmologic assessment of all participants, the strength of the DCVAS is its size and multi-site and multi-national setting, allowing for a robust and generalisable estimate of the occurrence of blindness in participants with GCA. Although blindness is a serious consequence of GCA and other individuals may have had loss of visual field or reduced visual acuity, this was not captured routinely as part of the study protocol and it is not possible to comment on the burden of less severe forms of sight loss.

5.4.0 CONCLUSIONS OF ESTIMATES OF PREVALENCE AND INCIDENCE

The datasets of GCANS, EPIC-Norfolk and DCVAS have provided new up-to-date incidence and prevalence estimates for PMR and GCA and absolute and relative risk for visual impairment amongst participants with GCA.

5.4.1 Prevalence of PMR and GCA in Norfolk

The GCANS study was not able to provide a prevalence estimate for PMR using the current EULAR/ACR criteria. However since the EULAR/ACR criteria require elevated inflammatory markers without stating a specific cut-point they are most similar to the criteria of Jones and Hazleman which require an ESR >30 mm/hr or CRP >6 mg/L. For GCANS the prevalence estimate for PMR fulfilling the Jones and Hazleman criteria was 1.53% (95% CI 1.20 to 1.87). For EPIC-Norfolk the prevalence estimate for cases fulfilling the EULAR/ACR criteria was 1.14% (95% CI 0.98%, 1.29%), lower than the last estimate of prevalence published by Kyle et al but comparable to the estimates published from the Mayo clinic (See Table 2.3).

The Norfolk-based datasets of GCANS and EPIC-Norfolk reveal a prevalence estimate for GCA fulfilling the 1990 ACR classification set of 0.25% (95% CI 0.11 to 0.39) and 0.29% (95% CI 0.21 to 0.36)

respectively. Similarly, in PMR the estimates are lower than the last UK study but in line with those published from the USA (See Table 2.3).

Current estimates of disease prevalence are important for public health planning. It is likely that the prevalence estimates for those studies, which have not defined disease by current classification criteria would be lower if they had. The estimates produced from the current work are comparable with estimates that have used similar methods and are from populations of Northern European heritage.

5.4.2 Incidence of PMR and GCA in Norfolk

Due to relatively small sample size GCANS was unable to provide an estimate for incidence rates. For EPIC-Norfolk the incidence rate per 100,000 for those cases fulfilling their current classification sets for PMR and GCA was 40.1 (95% CI 35.6, 45.2) and 11.2 (95% CI 9.0, 14.0) respectively. Again these figures are lower than for the UK CPRD study but in keeping with the estimates from the USA (See Table 2.4).

The estimates from EPIC-Norfolk have advantages in terms of being community-based and disease definitions using current classification criteria. They provide a greater certainty to the true rate of disease than the previously published estimates.

5.4.3 Prevalence of visual impairment in PMR and GCA

From the EPIC-Norfolk eye study, PMR does not appear to be associated with visual impairment compared to controls. There were eight (19.1%) individuals who had at one eye affected by visual impairment but no individual suffered from blindness. From the EPIC-Norfolk eye study the odds of visual impairment and low vision associated with GCA were OR = 4.10 (95% CI 1.44, 11.72 p = 0.008) and OR = 4.75 (95% CI 1.67, 13.54 p = 0.004) respectively. This was despite only comprising 42 cases, not separated by incident or prevalent disease. Restricting the estimate to only the 10 cases diagnosed with GCA prior to their eye assessment resulted in odds ratios for visual impairment and low vision of OR = 5.21 (95% CI 1.31, 20.77 p = 0.019) and OR = 6.03 (95% CI 1.52, 23.91 p = 0.011) respectively.

For the multi-national DCVAS, the rate of blindness in at least one eye was 7.9% amongst those participants with a diagnosis of GCA.

The previously published estimates for ocular morbidity are limited due to problems of case selection, variations in definition and standardisation for visual loss making interpretation difficult. The current estimates have many advantages in applying appropriate and standardised definitions to adequately defined cases of disease. In addition, despite the relatively small numbers, odds ratios of visual morbidity associated with diagnosis of PMR and GCA have been produced relative to appropriately matched

controls. These figures should prove useful for health care providers and planners.

CHAPTER 6 RISK FACTORS FOR ONSET

6.0 SUMMARY

This chapter documents risk factors associated with PMR and GCA disease onset. Of the three datasets, the data within EPIC-Norfolk is the most appropriate source to answer these questions due to the prospective study design and ability to adjust for confounders. The methods used for analysis comprise, crude and adjusted rate ratios from the incidence density, with subsequent logistic, then Cox regression.

Risk factors are assessed against those cases diagnosed in the cohort and subsequently, those fulfilling the current classification criteria sets.

6.1.0 EPIC-NORFOLK: RISK FACTORS ASSOCIATED WITH PMR AND GCA

The published aetiological factors for PMR and GCA have, in the main, been from studies using case-control design. Chapter 2.5.1 details the putative risk factors published to date, approaching these risk factors firstly by calculating incidence and rate ratios for age strata and for sex, with other risk factors recorded as part of the baseline health check. Logistic regression is used to assess the associations between baseline risk factors and incident diagnoses of PMR and or GCA.

Between 25th February 1993 to 13th May 1998, 25,660 healthy volunteers were recruited from 35 GP practice sites across Norfolk. The participants

were aged between 39 and 79 years with 14,052 women (54.8% of the cohort).

6.1.1 PMR diagnosis and association with age and sex

Cases of PMR were defined firstly as those over the age of 50 years at time of diagnosis and, secondly, those cases which met the current EULAR/ACR classification set. The analysis for cases of PMR and GCA was carried out separately, with those cases diagnosed with GCA converted to missing data so as not to contribute data as controls. PMR diagnosis was associated with age and female sex.

There were 395 cases of PMR diagnosed amongst a total baseline cohort of 25,542 participants at recruitment. Cases diagnosed with PMR who did not meeting the inclusion criteria were considered not be cases and contributed to the control pool, rather than being converted to missing data. Of these, 272 cases met the EULAR/ACR classification set amongst a total of 25,586 participants at baseline.

The odds ratio for each increase in age category (age in five year increments) was 1.06 (95%CI 1.05, 1.07 p=<0.0001). The crude rate ratio derived by the Mantel-Haenszel method for female sex was 2.29 (95% CI 1.83, 2.87 p=<0.0001). The Hazard Ratio (HR) derived using Cox regression was similar with a HR for the effect of females compared to males and PMR diagnosis of 2.29 (95% CI 1.83, 2.87, p=<0.0001).

Lexis expansion was used to analyse incidence rates for PMR cases across age bands and to compare rate ratios between men and women.

Table 6.1 Lexis expansion analysis for age at PMR diagnosis

Age band (years)	PMR cases (D) (n=395)	Person years follow-up (100,000 pyrs)	Rate per 100,000 pyrs	95% CI of rate
55-59	1	0.57	1.77	0.25, 12.54
60-64	5	0.71	7.04	2.93, 16.91
65-69	14	0.77	18.25	10.81, 30.82
70-74	41	0.70	58.80	43.30, 79.86
75-79	76	0.58	131.43	104.97, 164.56
80-89	186	0.50	370.74	321.12, 428.04
90+	72	0.03	2129.22	1690.07, 2682.47
Age band (years)	**PMR cases fulfilling EULAR/ACR criteria set (D) (n=272)**	**Person years follow-up (100,000 pyrs)**	**Rate per 100,000 pyrs**	**95% CI of rate**
55-59	1	0.57	1.77	0.25,12.54
60-64	3	0.71	4.22	1.36,13.10
65-69	7	0.77	9.13	4.35, 19.15
70-75	32	0.70	45.90	32.46, 64.90
75-79	47	0.58	81.23	61.07, 108.18
80-89	131	0.50	261.11	220.02, 309.89
90+	51	0.03	1508.20	1146.21, 1984.50

The incidence density of PMR for those aged 50 years or older was 89.7 (95% CI 81.3, 99.0) per 100,000 pyrs. Restricting the analysis to those 272 cases of PMR which fulfil the EULAR/ACR classification criteria set resulted in an incidence rate of 61.8 (95% CI 54.9, 69.6) per 100,000 pyrs at risk.

The effect of age on sex was analysed across age bands.

Table 6.2 comparing females to males by age band for PMR

Age band (years) PMR	Rate ratio	95% CI
55-59	Reference	N/A
60-64	3.12	0.35, 27.92
65-69	1.45	0.49, 4.33
70-74	3.40	1.57, 7.36
75-79	2.44	1.45, 4.11
80-89	2.03	1.46, 2.82
90+	1.34	0.80, 2.25
Overall effect of female sex controlling for age band	2.04	1.63, 2.56*
Age band (years) PMR EULAR/ACR criteria	**Rate ratio**	**95% CI**
55-59	Reference	N/A
60-64	1.56	0.14, 17.21
65-69	2.01	0.39, 10.38
70-74	2.47	1.11, 5.51
75-79	2.13	1.12, 4.04
80-89	2.28	1.52, 3.41
90+	1.51	0.80, 2.84
Overall effect of female sex controlling for age band	2.10	1.60, 2.77*

*chi^2 p=<0.0001

The age-adjusted effect (RR=2.04, 95%CI 1.63, 2.56) of female sex on diagnosis of PMR is the average effect across all subjects with no evidence (p=0.93) that the effect of female sex varies across the age band strata. An assumption of constant hazards is therefore justified and Cox regression appropriate although the effect is likely to be confounded by age since the crude rate ratio was 2.27.

6.1.2 GCA diagnosis and association with age and sex

Similar to the analysis of PMR cases, GCA cases were analysed separately from PMR.

There were 118 cases of GCA diagnosed over 50 years of age amongst a total baseline cohort of 25,265 participants at recruitment. Cases diagnosed with GCA not meeting the inclusion criteria were considered not be cases and contributed to the control pool rather than being converted to missing data. Of these 76 cases fulfilled the classification set amongst a total of 25,388 participants at baseline.

GCA diagnosis was associated with age and female sex. The odds ratio for each increase in age category (age in five year increments) was 1.05 (95%CI 1.03, 1.07 p=<0.0001). The crude rate ratio for female sex was 2.28 (95% CI 1.51, 3.45 p=0.0001) for all GCA cases over 50 years at diagnosis and 2.33 (95% CI 1.40, 3.92 p=0.001) for those fulfilling the ACR classification set.

Lexis expansion was used to analyse rate ratios for GCA cases across age bands.

Table 6.3 Lexis expansion analysis for age at GCA diagnosis

Age band (years)	GCA cases (D) (n=118)	Person years follow-up (100,000 pyrs)	Rate per 100,000 pyrs	95% CI of rate
55-59	1	0.57	1.77	0.25, 12.54
60-64	1	0.71	1.41	0.20, 10.00
65-69	10	0.77	13.04	7.02, 24.23
70-74	10	0.70	14.34	7.72, 26.66
75-79	17	0.58	29.40	18.28, 47.29
80-89	64	0.50	127.57	99.85, 162.98
90+	15	0.03	443.59	267.42, 735.80
Age band (years)	**GCA cases fulfilling ACR criteria set (D) (n=76)**	**Person years follow-up (100,000 pyrs)**	**Rate per 100,000 pyrs**	**95% CI of rate**
55-59	1	0.57	1.77	0.25,12.54
60-64	0	0.71	0.00	n/a
65-69	8	0.77	10.43	5.22, 20.86
70-74	5	0.70	7.17	2.99, 17.23
75-79	12	0.58	20.75	11.79, 36.54
80-89	40	0.50	79.73	58.48, 110
90+	10	0.03	295.73	159.12, 549.62

The incidence density of GCA for those aged 50 or older was 26.8 (95% CI 22.4, 32.1) per 100,000 pyrs. Restricting the analysis to those 76 cases of GCA which fulfil the ACR classification criteria set resulted in an incidence rate of 17.3 (95% CI 13.8, 21.6) per 100,000 pyrs at risk.

Assessing the effect of age on sex for a diagnosis of GCA, Table 6.4 compares rate ratios between females and males by age band.

Table 6.4 comparing females to males by age band for GCA

Age band (years) GCA	**Rate ratio**	**95% CI**
55-59	Reference	N/A
60-64	n/a	n/a
65-69	1.88	0.49, 7.27
70-74	7.42	0.94, 58.57
75-79	2.65	0.86, 8.12
80-89	1.81	1.16, 5.12
90+	1.42	0.45, 4.46
Overall effect of female sex controlling for age band	2.10	1.38, 3.15*
Age band (years) ACR GCA	**Rate ratio**	**95% CI**
55-59	Reference	N/A
60-64	n/a	n/a
65-69	2.42	0.49, 11.98
70-74	n/a	n/a
75-79	1.63	0.49, 5.41
80-89	2.44	1.16, 5.12
90+	0.78	0.22, 2.75
Overall effect of female sex controlling for age band	2.13	1.27, 3.55**

*chi^2 p=0.0003 **Chi^2 p=0.003

The age-adjusted effect (RR=2.10, 95%CI 1.38, 3.15) of female sex on diagnosis of GCA is the average effect across all subjects with no evidence (p=0.77) that the effect of female sex varies across the age band strata. However the effect is likely to be confounded by age since the crude rate ratio was 2.28.

6.1.3 PMR and GCA diagnoses and smoking status

The analysis of age and sex shows an effect for both of these and a diagnosis of PMR or GCA. In the logistic regression model both these

factors would need to be adjusted for in any estimates produced. The previous published studies find a positive association between PMR or GCA and smoking.

From the baseline data (see Table 5.5) 2,987 (11.7%) were current smokers, 10,766 (42.3%) former smokers and 11,687 (45.9%) never smokers. Data for smoking status was missing for 81 males and 139 females (0.86% of the cohort). Participants with GCA were more likely to have missing data for smoking: GCA cases over the age of 50 years 2.5% vs 0.86% overall and GCA cases meeting classification criteria set 4% vs 0.86%.

Due to the possibility that some current smokers may stop smoking a combined ever-smoker variable was created. Although it is possible that participants began smoking, the author believes this unlikely particularly given the age of the participants at baseline.

6.1.4 Smoking and its association with diagnosis of PMR

After adjusting for age at entry to the cohort and sex, ever-smoking was not associated with a diagnosis of PMR. For the PMR cases over the age of 50 years at diagnosis the OR = 0.95 (95% CI 0.77, 1.17, p=0.633) and for those PMR cases fulfilling the EULAR/ACR criteria OR = 1.16 (95% CI 0.89, 1.50 p=0.269).

6.1.5 Smoking and its association with a diagnosis of GCA

After adjusting for age at entry to the cohort and sex, ever-smoking was positively associated with a diagnosis of GCA. For the GCA cases over the age of 50 years at diagnosis the OR = 1.44 (95% CI 0.98, 2.11, p=0.060) and for those GCA cases fulfilling the 1990 ACR criteria OR = 1.44 (95% CI 0.89, 2.32 p=0.138). Re-coding as ever-smokers all those with missing data for smoking status resulted in OR of 1.47 (1.01, 2.15) p=0.045 and 1.50 (0.94, 2.41) p=0.091.

6.1.6 PMR and GCA diagnoses and vascular risk factors and modulators of endothelial dysregulation

Chapter 2.5.1 lists the aetiological factors published to date. The analysis of age at diagnosis and sex confirmed these as important factors associated with diagnoses of PMR and GCA, therefore any subsequent model is adjusted for these factors. Table 6.5 lists the univariate analysis using logistic regression, adjusting for age and sex at baseline.

Table 6.5 Logistic regression analysis - Univariate analysis of traditional cardiovascular risk factors and their association to PMR and GCA diagnoses within the EPIC-Norfolk cohort

Characteristic*	PMR (n=395)	PMR ACR/EULAR (n=272)	GCA (n=118)	GCA ACR (n=76)
Ever smoking	0.95 (0.78, 1.17) p=0.643	0.90 (0.70, 1.15) p=0.407	1.44 (0.98, 2.11) p=0.06	1.44 (0.89, 2.32) p=0.138
Self-reported high blood pressure	0.91 (0.70, 1.17) p=0.451	0.95 (0.69, 1.29) p=0.732	0.88 (0.55, 1.40) p=0.593	0.63 (0.37, 1.07) p=0.087
Systolic BP >140 mm/Hg	1.00 (0.81, 1.24) p=0.980	0.91 (0.70, 1.17) p=0.463	0.65 (0.44, 0.97) p=0.036	0.79 (0.48, 1.28) p=0.336
Diastolic BP >90 mm/Hg	1.24 (0.99, 1.55) p=0.064	1.12 (0.89, 1.53) p=0.272	0.80 (0.51, 1.26) p=0.338	1.06 (0.62, 1.79) p=0.839
HDL <1.0 mmol/L	0.57 (0.35, 0.93) p=0.024	0.59 (0.33, 1.04) p=0.066	0.97 (0.48, 1.97) p=0.938	0.83 (0.33, 2.11) p=0.698
LDL >4.1 mmol/L	1.34 (1.08, 1.66) p=0.008	1.37 (1.07, 1.77) p=0.014	1.20 (0.82, 1.77) p=0.350	1.46 (0.90, 2.37) p=0.124
LDL/HDL ratio >2.5	1.20 (0.95, 1.50) p=0.122	1.32 (1.01, 1.73) p=0.045	1.18 (0.78, 1.79) p=0.422	1.30 (0.77, 2.19) p=0.321
Triglycerides >2.2 mmol/L	0.86 (0.68, 1.10) p=0.224	0.89 (0.67, 1.18) p=0.423	1.06 (0.69, 1.61) p=0.796	0.85 (0.49, 1.48) p=0.563
Self-reported diabetes	1.50 (0.70, 3.18) p=0.297	1.43 (0.59, 3.49) p=0.433	1.51 (0.37, 6.13) p=0.569	0.95 (0.23, 3.88) p=0.938
BMI >30 kg/m^2	0.83 (0.62, 1.10) p=0.198	0.71 (0.50, 1.03) p=0.067	0.63 (0.35, 1.12) p=0.116	0.60 (0.29, 1.25) p=0.174
hs-CRP >2.6 mg/L	1.18 (0.93, 1.50) p=0.184	1.18 (0.92, 1.52) p=0.198	1.45 (0.95, 2.22) p=0.082	2.11 (1.25, 3.58) p=0.006

Data presented are odds ratios with 95% CI and p values. *Adjusted for age and sex at baseline. Self-reported diagnoses are from baseline questionnaire at time of recruitment. BP – Blood pressure, LDL – Low-density lipoprotein, HDL – high-density lipoprotein, BMI – Body mass index, hs-CRP – high sensitivity CRP (measured from a range of 0 to 160 mg/L with values outside this range converted to missing data).

The logistic regression analysis revealed a positive association between serum levels of LDL cholesterol above 4.1 mmol/L and subsequent diagnoses of PMR. GCA was positively associated with a raised hs-CRP of greater than 2.6 mg/L. As the presence of raised inflammatory markers may be the result of the inflammatory process of GCA at time of disease development, all cases of GCA with a diagnosis made within a year of serum hs-CRP were excluded. This resulted in 11 cases of GCA being excluded of whom three were excluded from those defined by the ACR criteria set. This resulted in an adjusted odds ratio associated with hs-CRP >2.6 mg/L of 1.44 (0.93, 2.22) p=0.102 for all cases of GCA over 50 years of age and 2.13 (1.24, 3.65) p=0.006 for those meeting the ACR classification criteria set.

A multivariate logistic model was used to estimate the odds ratios for PMR and GCA cases incorporating a number of variables and possible confounders (See table 6.6).

Generally, raised systolic blood pressure and BMI of > 30 kg/m^2 was associated with an odds ratio of below one for both PMR and GCA but failed to reach statistical significance apart from systolic BP >140 mm/Hg and GCA and BMI > 30 kg/m^2 and PMR. Logistic regression analyses revealed these factors to be associated with death. Competing risk analysis was used to explore this relationship further using the Fine-Gray method (222).

Table 6.6 Logistic Regression analysis multivariable modelling

Logistic Regression model	Variable	PMR50 OR (95% CI) p value (n=22,923)	PMR EULAR/ACR OR (95% CI) p value (n=22,961)
age, sex, LDL, diastolic BP	age	1.06 (1.05, 1.07) p <0.001	1.06 (1.04, 1.07) p <0.001
	sex	2.44 (1.91, 3.10) p <0.001	2.61 (1.96, 3.48) p <0.001
	LDL >4.1 mmol/L	1.31 (1.05, 1.62) p = 0.015	1.35 (1.05, 1.74) p = 0.021
	diastolic BP >90 mm/Hg	1.18 (0.93, 1.51) p = 0.169	1.12 (0.85, 1.49) p = 0.420
age, sex, LDL, diastolic BP with interaction term for LDL and sex	age	1.06 (1.05, 1.07) p <0.001	1.06 (1.04, 1.07) p <0.0001
	sex	2.31 (1.65, 3.23) p <0.001	2.75 (1.83, 4.14) p<0.0001
	LDL >4.1 mmol/L	1.21 (0.80, 1.83) p = 0.373	1.46 (0.89, 2.40) p = 0.136
	diastolic BP >90 mm/Hg	1.18 (0.93, 1.50) p = 0.171	1.13 (0.85, 1.50) p = 0.417
Logistic Regression model	**Variable**	**GCA50 OR (95% CI) p value (n=18,004)**	**GCA ACR OR (95% CI) p value (n=18,022)**
age, sex, ever smoking, hs-crp	age	1.06 (1.03, 1.08) p<0.001	1.05 (1.02, 1.08) p-0.002
	sex	2.72 (1.65, 4.48) p<0.001	2.71 (1.45, 5.08) p=0.002
	ever smoking	1.67 (1.06, 2.65) p=0.028	1.52 (0.87, 2.68) p=0.144
	hs-crp >2.6 mg/L	1.41 (0.91, 2.19) p=0.127	2.13 (1.24, 3.68) p=0.007
age, sex, ever smoking, hs-crp with interaction term for ever smoking and sex	age	1.06 (1.03, 1.08) p<0.001	1.05 (1.02, 1.08) p=0.002
	sex	2.31 (0.89, 6.04) p=0.087	1.36 (0.50, 3.73) p=0.550
	ever smoking	1.41 (0.52, 3.83) p=0.506	0.70 (0.23, 2.10) p=0.521
	hs-crp >2.6 mg/L	1.41 (0.91, 2.19) p=0.124	2.17 (1.26, 3.75) p=0.006

PMR model: total cohort (n=25,542) missing data for LDL (n=2578) and diastolic bp (n=84). Likelihood ratio tests between models: chi^2 p value 0.6589 and 0.7173 respectively no evidence of an interaction between LDL and sex. GCA model: total cohort (n=25,265) missing data for hs-crp (n=7,113) and ever smoking (n=217). Likelihood ratio tests between models: chi^2 p=0.7093 and 0.1344 respectively no evidence for an interaction between ever smoking and sex.

6.1.7 Competing risk analysis for death and diagnoses of PMR and GCA

Survival methods were used to test aetiological factors associated with disease outcome. Due to the longitudinal data within EPIC-Norfolk and the dynamic nature of the cohort due to the long enrolment period, and ability to test several covariates, Cox regression is an appropriate analytical model. A Cox proportional hazards model was created including age, sex and the dichotomised diastolic hypertension variable used to test the association to PMR. The resultant hazard ratios were 2.02 (95% CI 1.61, 2.53) for female sex after adjusting for age and after including the diastolic hypertension variable was 2.04 (95%CI 1.62, 2.56). The graphic outputs did not reveal a violation of the proportional hazard assumption and this was supported by a non-significant p value based on a Chi^2 test of the Schoenfeld residuals, again supporting no violation of the proportionality assumption.

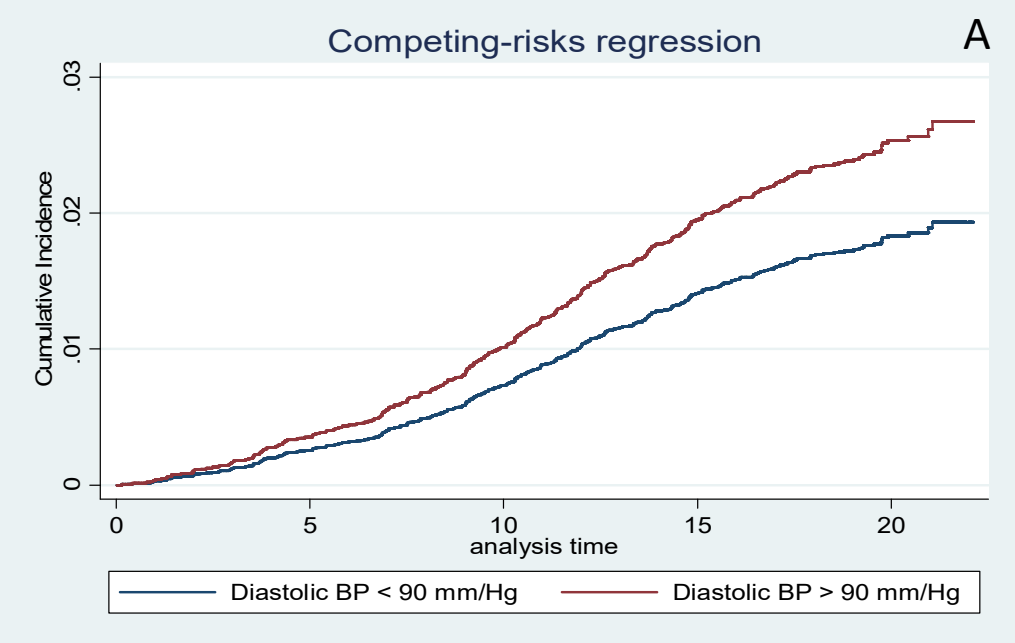
Due to the strong association between age and diagnoses of PMR and GCA, it is possible that there is competing risk with death. As traditional cardiovascular risk factors are known to increase the risk of death, the risk factors used in the logistic regression analysis may therefore be confounded by death.

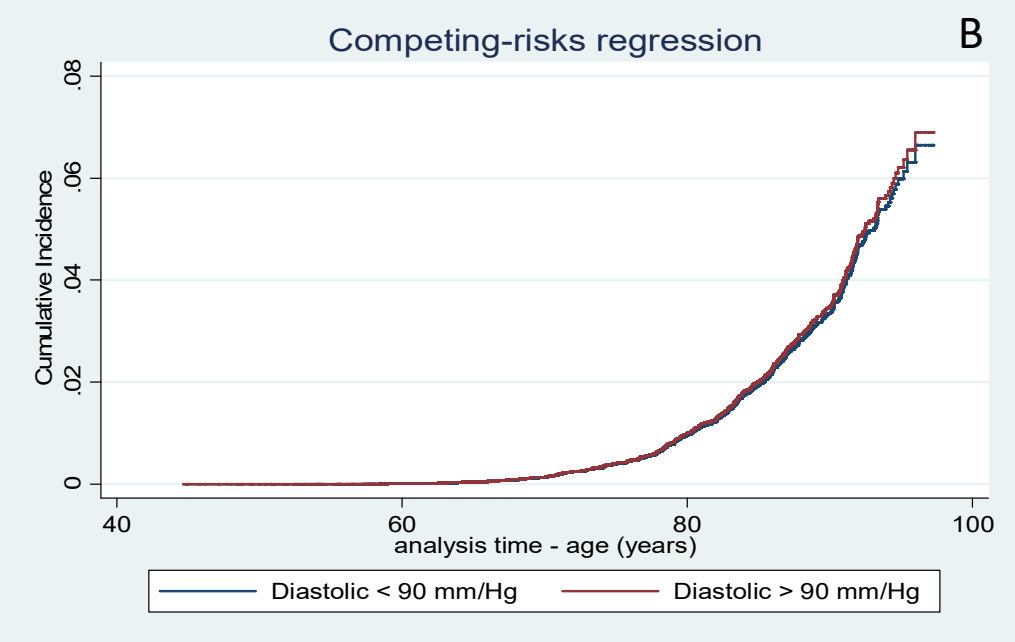
Survival analysis techniques were used to assess risk factors for subsequent PMR and GCA diagnoses with a competing risk for death. Cox

regression with a Fine-Gray extension was used to produce the following cumulative incidence function diagrams for the putative risk factors and subsequent diagnoses of PMR and GCA. This was firstly carried out adjusting for duration of follow-up time and subsequently for age, with PMR defined as those with the condition diagnosed over 50 years of age with baseline diastolic blood pressure as a predictive variable. (See Figure 6.1). Figure 6.1 panel A, shows a separation between the lines of those at baseline with a diastolic blood pressure of greater than 90 mm/Hg having an increased risk for PMR. The lines follow similar profiles by the dichotomised diastolic blood pressure variable, with no apparent violation of the proportional hazards assumption. However since the logistic regression analysis (Table 6.6) showed no association when adjusting for age, the Cox proportional model with competing risk for death was set using participants' date of birth as the origin, rather than entry to the cohort at the time of recruitment. This analysis displayed in Panel B shows no association between the dichotomised diastolic blood pressure variable and subsequent risk of PMR. This analytical exercise reveals the importance of age as a confounder in the risk for both PMR and increased diastolic blood pressure. As a consequence all subsequent Cox-proportional models were set with date of birth as the origin, with competing risk for death. Figures 6.2 and 6.3 show the cumulative incidence plots for cases of PMR and GCA defined firstly by those older than 50 years at diagnosis and those meeting the current classification

criteria set. The risk factors identified from the logistic regression analysis are re-analysed using Cox regression with competing risk for death.

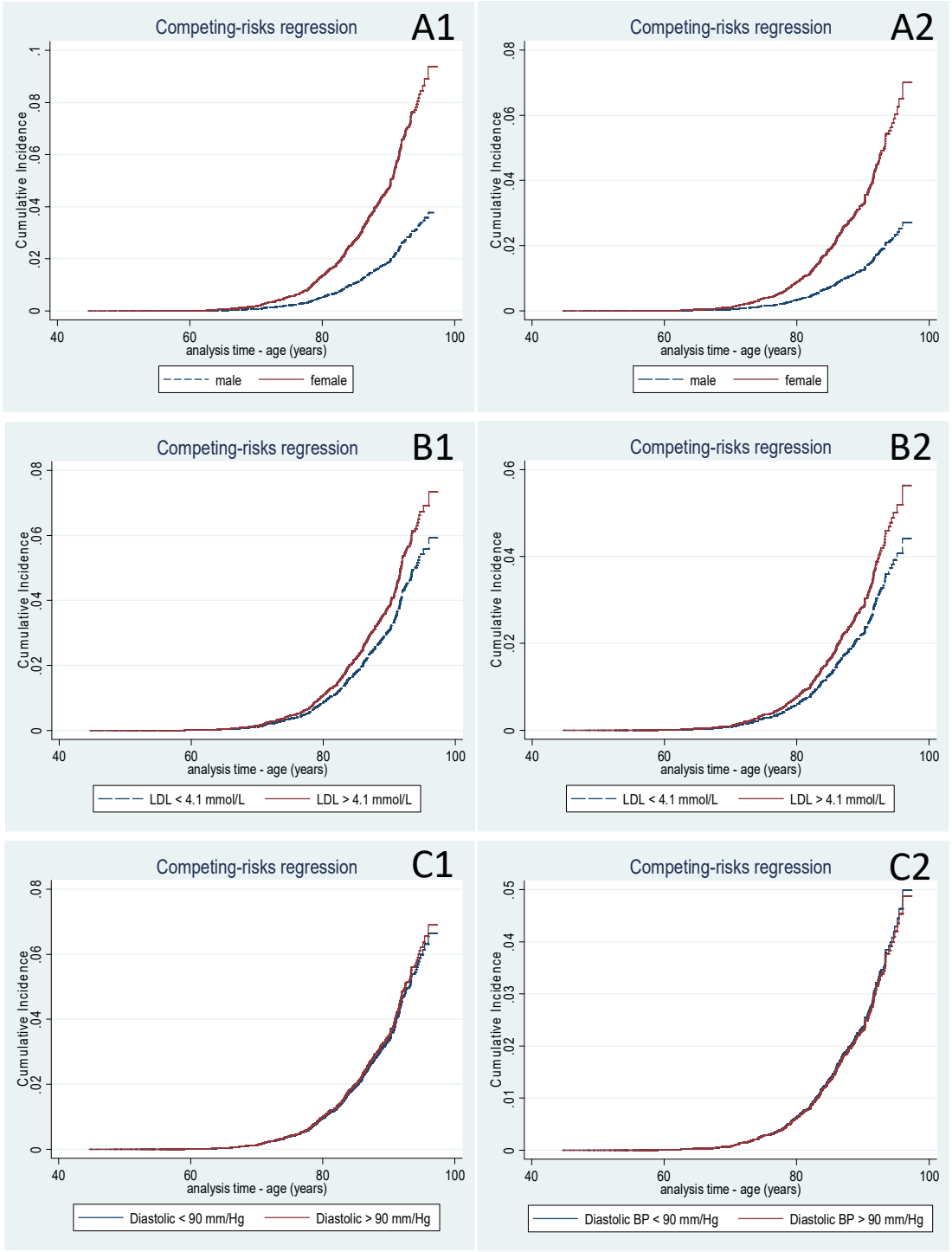
Figure 6.1 Cox regression with competing risk for death for PMR diagnosis





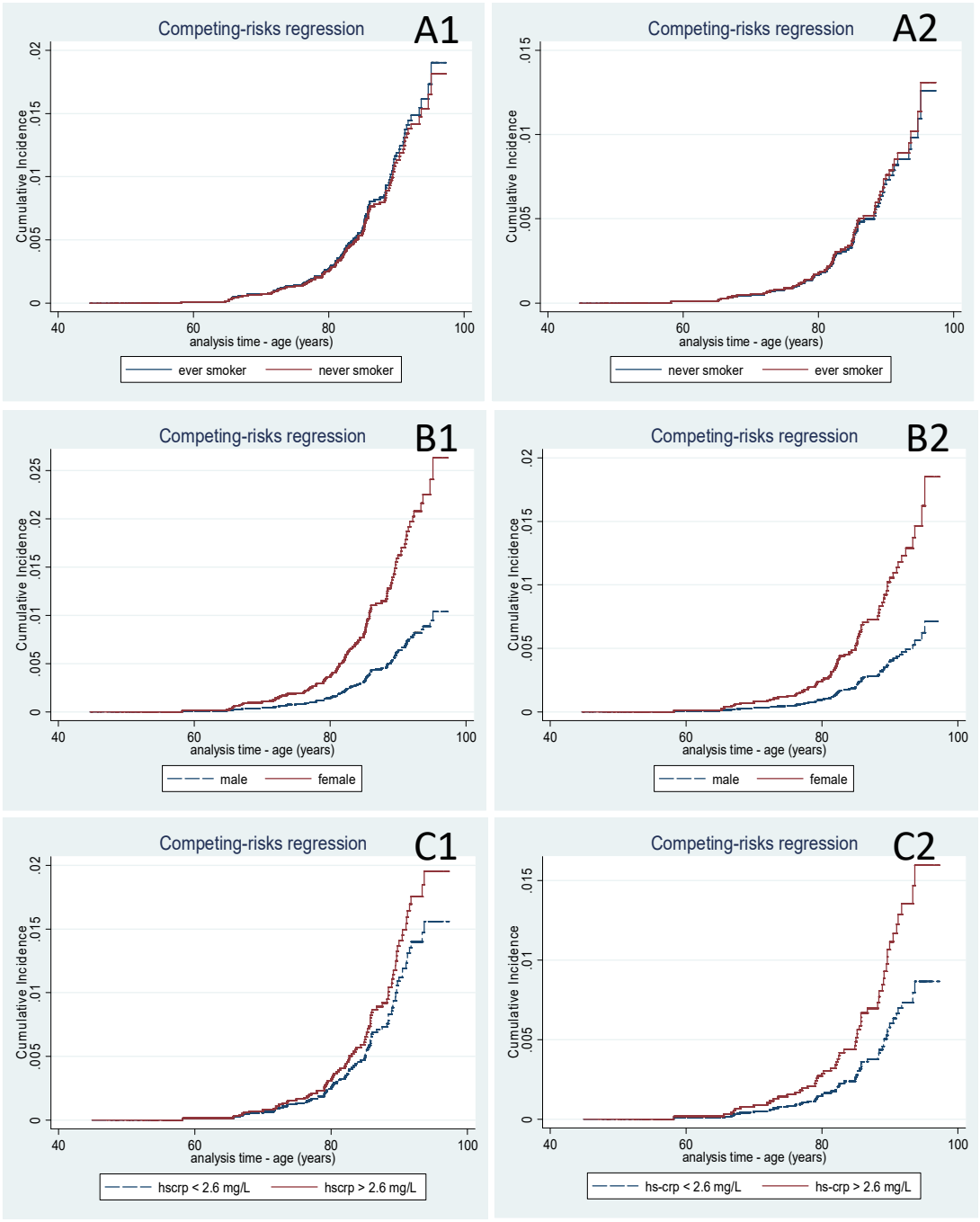
The above figure are from Cox regression with competing risk for death showing cumulative incidence of PMR diagnosis within the EPIC-Norfolk cohort. Panel A is stratified from time at entry to the cohort and panel B accounting for age by using date of birth as the origin in the analysis.

Figure 6.2 Cox regression with competing risk for death, predictors of PMR



The above panel diagram shows predictors of PMR from baseline assessment. Figures A1, B1 and C1 are by cases of PMR diagnosed over the age of 50, with A2, B2 and C2 defined by EULAR/ACR criteria. Panel A assess the effect of sex, B the effect of LDL and C the effect of raised diastolic blood pressure.

Figure 6.3 Cox regression with competing risk for death, predictors of GCA



The above panel diagram shows predictors of GCA from baseline assessment. Figures A1, B1 and C1 are by cases of GCA diagnosed over the age of 50, with A2, B2 and C2 defined by ACR 1990 criteria. Panel A assess the effect of smoking, B the effect of sex and C the effect of high-sensitivity CRP.

The results from the Cox regression with competing risk for death reveal similar risk factors to the logistic regression modelling for PMR and GCA diagnosis.

For PMR (See Figure 6.2), an increased risk was associated with an LDL of greater than 4.1 mmol/L at baseline, with those cases of PMR aged greater than 50 years having a sub-hazard ratio (SHR) of 1.25 (95% CI 1.02, 1.54) p = 0.036 and those meeting the EULAR/ACR classification criteria a SHR of 1.29 (95% CI 1.01, 1.64) p = 0.043. Female sex resulted in a sub-hazard ratios of 2.56 (95% CI 2.04, 3.21) p < 0.0001 and 2.64 (95% CI 2.00, 3.47) p <0.0001 respectively by those cases defined by age and those meeting classification criteria.

For GCA (See Figure 6.3), despite a signal for ever-smoking in cases defined over the age of 50 years at diagnosis using logistic regression, no similar increased risk was not found using Cox regression and competing risk for death. The resultant SHRs for ever-smoking were 1.05 (95% CI 0.72, 1.53) p = 0.25 and 1.04 (95% CI 0.65, 1.67) p = 0.16 by cases defined over the age of 50 years at diagnosis and those meeting the current classification criteria respectively. For high-sensitivity CRP, all cases diagnosed within a year of serum assessment were excluded from the analysis. This resulted in SHRs of 1.26 (95% CI 0.82, 1.93) p = 0.298 and 1.85 (95% CI 1.09, 3.14) p = 0.022 respectively. Similarly as for PMR, female sex resulted in SHRs of 2.56 (95% CI 1.69, 3.87) p < 0.0001 and 2.61 (1.56, 4.39) p < 0.0001 respectively.

6.1.8 PMR and GCA diagnoses and genetic risk factors

Several GWAS studies have been published assessing the genetic contribution of SNPs to diagnoses of PMR and GCA. The strongest and most consistent associations have been found with *HLA-DRB1*0401*. SNP analysis was carried out on the EPIC-Norfolk cohort. The SNP rs6910071, as a tag of HLA-DRB1, has been reported previously to be associated with both conditions, with greatest risk associated with the A allele (223, 224).

The logistic regression analysis revealed an odd ratio of 1.57 (1.33, 1.85) p=<0.0001 for PMR cases defined by the age cut-off and 1.47 (1.21, 1.79) p<0.001 for those meeting the PMR classification set.

For GCA the logistic regression analysis revealed an odd ratio of 1.39 (1.01, 1.91) p=0.044 for GCA cases defined by the age cut-off and 1.43 (0.96, 2.12) p=0.075 for those meeting the GCA classification set. The results remained very similar with adjustment for age and sex at baseline.

6.1.9 Comments

The factors associated with greatest risk for PMR and GCA are increasing age and female sex, in keeping with the published literature. This is the first time that a prospective cohort study design has been used to explore

risk factors for PMR and GCA development and to apply current classification criteria.

Analysis of traditional cardiovascular risk factors firstly with logistic regression then Cox proportional hazards with Fine Gray extension, resulted in associations between raised LDL (>4.1 mmol/L) and PMR and raised hs-crp (>2.6 mg/L) and GCA. Due to the possibility of raised inflammatory markers being a manifestation of undiagnosed GCA, all cases of GCA diagnosed within a year of hs-CRP assessment were excluded from the analysis.

Analysis for diastolic blood pressure suggested a possible signal associated with PMR when using logistic regression, but this was nullified when using Cox proportional hazards and competing risk for death. It is possible that many more participants developed hypertension during follow-up, with analysis based only on baseline data resulting in a spurious non-significant association. However, it is impossible to speculate further without data for blood pressure at later time points.

In agreement with previously published data, the greatest risk estimates for PMR and GCA are increasing age and female sex. It is still possible that the associations are chance findings, but others have found similar associations and the major strength of the prospective study design reduces the risk of Type I error through reductions of recall and selection biases. The EPIC-Norfolk cohort has allowed for robust phenotypic analysis and use of classification criteria in case definition.

CHAPTER 7 INFLUENCE OF MEDICATION PRIOR TO DIAGNOSIS OF PMR AND GCA

7.0 SUMMARY

Several studies have assessed the effect of statins and their influence in GCA development and outcome. The Cox regression analysis revealing an effect of LDL and subsequent PMR diagnosis. In keeping with a cardiovascular dysfunction aetiological mechanism further analysis was carried out using the EPIC-Norfolk cohort and baseline questionnaire data for several medications used to treat cardiovascular disease and its risk factors namely hypertension and hyperlipidaemia. The baseline questionnaire asked in question 12: "*In the last week, have you taken any drugs or medicines either prescribed by your doctor or bought from the chemist? (Please include inhalers, pain killers etc.).* See Table 7.1 for details of medication recorded for the various case definitions and controls.

Table 7.1 Medication at baseline by subsequent PMR and GCA diagnosis

Medication from baseline questionnaire	PMR50 (n=395)	PMR EULAR/ACR (n=275)	GCA50 (n=118)	ACR GCA (n=76)	Controls (n=25,147*)
Anti-hypertensives n,(%)	90 (22.8)	62 (22.8)	31 (26.3)	20 (26.3)	4,701 (18.7)
ACE-inhibitors n,(%)	8 (2.0)	6 (2.2)	4 (3.4)	3 (4.0)	804 (3.2)
Calcium-channel blockers n,(%)	27 (6.8)	19 (7.0)	8 (6.8)	4 (5.3)	1,407 (5.6)
Beta-blockers n,(%)	30 (7.6)	19 (7.0)	10 (8.5)	7 (9.2)	1,581 (6.3)
Lipid-lowering medication n,(%)	11 (2.8)	7 (2.6)	2 (1.7)	1 (1.3)	369 (1.5)

Collected from baseline questionnaire at time of recruitment. *Controls are for the PMR and GCA cases defined by age greater than 50 years at time of diagnosis but the overall percentages by drug class do not vary amongst the controls by the various case definitions.

7.1.0 Hypertension and its definition

Not everyone with hypertension will be prescribed treatment. To assess the differences in hypertension definition and subsequent disease outcome, the various questions relating to hypertension and its treatment are presented in the cross tabs below (Table 7.2). Of those prescribed anti-hypertensives, 51.5% had systolic blood pressure above 140 mm/Hg at their baseline health check attendance, and those who reported having high blood pressure, 78.0% stated they were on medication. Using all three definitions (i.e. if at least one definition was affirmative), 11,769 (45.9%) participants within the cohort had high blood pressure: either self-declared hypertension; were on treatment or had a systolic BP of > 140 mm/Hg (average of two readings).

Table 7.2 Agreement in definitions of Hypertension amongst EPIC-Norfolk participants at baseline

	Systolic BP > 140mm/Hg	Self-reported high BP	Anti-hypertensives
Systolic BP >140mm/Hg (n = 9,166)		25.1%	27.1%
Self-reported high BP (n =3,671)	62.7%		78.0%
Anti-hypertensives (n = 4,822)	51.5%	59.4%	

For example of those with a raised systolic blood pressure of > 140 mm/Hg, 25.1% self-reported having high blood pressure and 27.1% declared they were taking anti-hypertensive medication.

Table 7.2 shows the various definitions for hypertension. The greatest agreement was between those who reported hypertension and were on anti-hypertensives, however of those on treatment 51.5% were hypertensive when having their blood pressure measured.

From Chapter 6.1.6 and Table 6.5 defining hypertension by self-declared diagnosis or baseline blood pressure measurement was associated with reduced odds for PMR and GCA although few estimates reached statistical significance.

Recalculation using Cox proportional hazards with competing risk for death, adjusted for age and sex, resulted in the following estimates using the combined hypertension variable: PMR50 SHR = 0.83 (0.68, 1.01) p = 0.06, PMR EULAR ACR classified cases SHR = 0.77 (0.60, 0.97) p = 0.03, GCA50 SHR = 0.59 (0.41, 0.85) p = 0.005 and ACR classified cases of GCA SHR = 0.69 (0.44, 1.09) p = 0.111. Most of the results reveal a reduced risk amongst individuals with the combined hypertension variable, which could be due to contribution from medication modifying the risk.

7.1.1 Anti-hypertensives

The baseline questionnaire recorded all anti-hypertensive agents, irrespective of class. From Table 7.1 not all participants could remember the class or precise name of their anti-hypertensive agent so there are a number of participants whose class of medication is unknown. At least

70% of those with PMR or GCA and 80% of controls did report their class of anti-hypertensive.

Cox-proportional hazards with competing risk for death, adjusted for age and sex was calculated for anti-hypertensive medication with the results displayed in Table 7.3

Table 7.3 Anti-hypertensive medication and subsequent risk for PMR and GCA diagnosis

Medication at baseline from questionnaire	PMR50 (n=395)	PMR EULAR/ACR (n=272)	GCA50 (n=118)	GCA ACR (n=76)
Anti-hypertensives, SHR (95% CI)	0.72 (0.57, 0.91) p = 0.006	0.72 (0.54, 0.95) p = 0.020	0.90 (0.60, 1.36) p = 0.625	0.91 (0.55, 1.51) p = 0.705
ACE-inhibitors, SHR (95% CI)	0.46 (0.23, 0.92) p = 0.029	0.50 (0.22, 1.12) p = 0.093	0.80 (0.30, 2.18) p = 0.665	0.94 (0.30, 3.00) p = 0.919
Calcium-channel blockers, SHR (95% CI)	0.77 (0.52, 1.14) p = 0.186	0.78 (0.49, 1.25) p = 0.302	0.79 (0.39, 1.60) p = 0.504	0.60 (0.22, 1.64) p = 0.319
Beta-blockers, SHR (95% CI)	0.80 (0.55, 1.16) p = 0.239	0.73 (0.46, 1.16) p = 0.177	0.92 (0.48, 1.76) p = 0.800	1.01 (0.46, 2.21) p = 0.980

7.1.2 Lipid lowering drugs

The results for baseline serum LDL > 4.1 mmol/L revealed an increased sub-hazard ratio for subsequent PMR diagnosis (See chapter 6.1.7). Relatively few participants taking lipid lowering drugs were subsequently diagnosed with PMR or GCA. The results of the Cox-proportional hazard with competing risk for death and adjusting for age and sex revealed the following sub-hazard ratios: PMR50 SHR = 1.39 (0.76, 2.51) p = 0.284, PMR EULAR ACR classified cases SHR = 1.27 (0.60, 2.69) p = 0.531, GCA50 SHR = 0.85 (0.21, 3.39) p = 0.812 and ACR classified cases of GCA SHR = 0.66 (0.09, 4.70) p = 0.674.

7.1.3 Comments

The combined hypertension variable resulted in reduced risk for later diagnosis of PMR and GCA. It is important to note that this exposure was collected at baseline with PMR and GCA diagnosed during the following 20 years. Not all those with hypertension measured at baseline were on treatment and this is likely to have changed over follow-up. In addition, changes in national guidance may have affected the choice of agent offered over the follow-up period with the joint NHS and British Hypertension Society guidelines being published in 2006. Subsequently ACE-I became the most commonly prescribed agent having previously been beta-blockers (225). Prescription of anti-hypertensives lowered the risk for PMR and although the estimate for GCA, was similarly protective,

this did not reach statistical significance. It is possible that those identified with hypertension started treatment resulting in their apparent reduction in risk but this cannot be ascertained from the data available.

CHAPTER 8 RISK FACTORS ASSOCIATED WITH PROGRESSION

8.0 Summary

The risk factors associated with blindness in GCA and inflammatory polyarthritis in PMR were investigated using DCVAS and EPIC-Norfolk datasets. DCVAS due to its set-up of recruiting cases and comparator conditions allowed to compare factors associated with blindness amongst cases of GCA using logistic regression to calculate odds ratios. EPIC-Norfolk with its prospective study design enabled use of survival methods in this case Cox-proportional hazards with a Fine-Gray extension to assess baseline clinical features associated with subsequent diagnosis of inflammatory polyarthritis.

8.1.0 RISK FACTORS ASSOCIATED WITH BLINDNESS IN DCVAS

In those recruited to DCVAS, descriptive statistics were used to assess patient characteristics and their association to blindness, with standard nonparametric tests used to assess differences between groups. Previous studies have found an association between laboratory markers and subsequent blindness, including relatively lower inflammatory markers, anaemia and thrombocytosis (58, 198, 199). For these reasons inflammatory markers: Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), and haematological tests: anaemia – haemoglobin (Hb)

<100 g/L and platelets > 500 x 10^9/L were assessed for their association with subsequent blindness

8.1.1 Analytical approach

Previous data have suggested a relationship between prior vascular disease and ischaemic complications in GCA. A logistic regression analysis was applied to examine the strength of the association between vascular risk factors with blindness at six months, recorded as odds rations (OR) with 95% confidence intervals (CI). In a sensitivity analysis, the models were recalculated, firstly using the 1990 ACR criteria set and secondly positive temporal artery biopsy (TAB) findings to define GCA diagnosis.

8.1.2 Laboratory values at diagnosis and risk of blindness

Patients who developed blindness had a lower CRP at presentation (Table 6.7); however, no other clinical feature of GCA itself was significantly associated with blindness at six months.

Table 8.1 Baseline characteristics

Clinical Features	Physician Diagnosis of GCA at 6 months (>75% certainty) n=433		
	Blind at six months (n=34)	Not blind at six months (n=399)	p value*
Age at diagnosis (median, years)	74.9	73.0	0.073
Male (%)	12 (35.3)	133 (33.3)	0.816
New-onset headache	23 (67.7)	282 (70.7)	0.710
Any visual symptom (%)	32 (94.1)	154 (38.6)	0.000
Jaw claudication (%)	13 (38.2)	163 (40.9)	0.766
Tongue claudication (%)	3 (8.8)	16 (4.0)	0.188
Morning stiffness shoulders arms (%)	7 (20.6)	87 (21.8)	0.869
Morning stiffness hips/thighs (%)	5 (14.7)	69 (17.3)	0.700
Myalgia (%)	5 (14.7)	109 (27.3)	0.109
Fever (%)	3 (8.8)	68 (17.0)	0.214
Fatigue (%)	13 (38.2)	164 (41.1)	0.744
Weight loss (%)	12 (35.3)	138 (34.6)	0.934
Smoking Status			
Current (%)	4 (14.0)	56 (11.8)	0.741
Former (%)	9(31.1)	124 (26.5)	0.741
Never (%)	21 (54.9)	219 (61.8)	0.741
Comorbidities			
Coronary heart disease (%)	2 (5.9)	27 (6.8)	0.843
Heart failure (%)	0 (0.0)	9 (2.26)	0.376
Peripheral vascular disease (%)	5 (14.7)	6 (1.5)	0.000
Hypertension requiring therapy (%)	15 (44.1)	164 (41.1)	0.732
Diabetes mellitus (%)	7 (20.6)	33 (8.3)	0.017
Cerebrovascular accident (%)	4 (11.8)	10 (2.5)	0.003
Dyslipidaemia (%)	10 (29.4)	87 (21.8)	0.307
Chronic obstructive Pulmonary disease	0 (0.0)	24 (6.0)	0.141
Laboratory test results at presentation (%)			
Positive temporal artery biopsy	23 (67.7)	203 (50.9)	0.060
Median ESR mm/hr	65	70	0.620
Median CRP mg/L	46	64	0.025
Anaemia (Haemoglobin <100g/L) (%)	4 (11.8)	62 (15.5)	0.803
Thrombocytosis (platelets > 500 x 10^9/L) (%)	3 (8.8)	75 (18.8)	0.330

*p-value of difference between those who were subsequently declared blind in at least one eye versus those who were not; all calculated using the chi squared test except for median age at diagnosis, ESR and CRP which was tested by the Mann-Whitney test. GCA: giant cell arteritis; ESR: erythrocyte sedimentation rate; CRP: C - reactive protein.

8.1.3 Vascular disease and blindness

Table 6.8 shows the results of logistic regression analysis, examining associations between potential vascular risk factors assessed at baseline and blindness (adjusted for age and sex). Factors positively associated with blindness at six months included i) a prior history of cerebrovascular accident (CVA) (OR = 4.47, 95% CI: 1.30 to 15.41), and ii) peripheral vascular disease (PVD) (OR = 10.44, CI: 2.94 to 37.03). There was no association between baseline laboratory findings and blindness.

With the sensitivity analysis, the findings were largely unchanged: rates of blindness in those meeting the 1990 ACR criteria and those with a positive TAB were 7.4% and 9.8%, respectively. The associations between PVD and CVA remained statistically significant with positive associations for blindness at six months (for PVD, ACR cases OR = 9.40, (2.14 to 41.34), TAB positive cases OR = 9.22, (1.56 to 54.70), for CVA, ACR cases OR = 5.29, (95% CI 1.39 to 20.07), TAB positive cases OR = 4.02, (0.89 to 18.16)). The association between prevalent diabetes mellitus and blindness reached statistical significance for those cases defined by positive TAB (4.28, CI: 1.42 to 12.92) although not the cases defined by 1990 ACR criteria (2.24, CI: 0.84 to 5.96).

Table 8.2 Association between vascular disease factors assessed at presentation and blindness at 6 months

Presenting features	Physician Diagnosis of GCA at 6 months (>75% certainty) n=433		1990 ACR Criteria cases n=404	TAB positive cases n=235
	Unadjusted OR, 95% CI	Adjusted* OR, 95% CI	Adjusted* OR, 95% CI	Adjusted* OR, 95% CI
BMI†	1.10, (1.01 to 1.19)	1.10, (1.02 to 1.20)	1.10, (1.00 to 1.21)	1.13, (1.00 to 1.28)
Smoking (ever vs never)	0.75, (0.37 to 1.55)	0.78, (0.36 to 1.68)	0.65, (0.28 to 1.54)	0.70, (0.26 to 1.84)
Cardiovascular disease at baseline	0.86, (0.20 to 3.79)	0.77, (0.17 to 3.45)	0.77, (0.16 to 3.58)	2.02, (0.38 to 10.78)
Diabetes at baseline	2.88, (1.16 to 7.10)	2.48, (0.98 to 6.25)	2.26, (0.82 to 6.17)	4.19, (1.39 to 12.67)
Stroke at baseline	5.19, (1.54 to 17.53)	4.47, (1.30 to 15.41)	5.29, (1.39 to 20.07)	4.02, (0.89 to 18.16)
Peripheral vascular disease at baseline	11.29, (3.25 to 39.23)	10.44, (2.94 to 37.03)	9.40, (2.14 to 41.34)	9.22, (1.56 to 54.70)
Hyperlipidaemia at baseline	1.49, (0.69 to 3.24)	1.45, (0.67 to 3.15)	1.43, (0.62 to 3.29)	2.20, (0.87 to 5.60)
Hypertension on medication at baseline	1.13, (0.56 to 2.29)	0.99, (0.48 to 2.03)	1.11, (0.51 to 2.39)	0.73, (0.30 to 1.79)

*Adjusted for age and sex. †Missing data for BMI (n = 131). GCA: giant cell arteritis; OR: odds ration; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C -reactive protein.

8.1.4 Comments

The DCVAS data are international and therefore should be widely generalisable but potentially could be biased due to being sampled from secondary and tertiary care centres. In keeping with previous published data on GCA, the DCVAS participants were similar in terms of their age at diagnosis and in that 288 of the 433 (66.5%) were women. A formal recording of visual performance was not made for all individuals in DCVAS and therefore a hard, but relatively severe, definition of blindness was used, captured as part of the VDI assessment. Finally, the results from the analysis of BMI should be interpreted cautiously due to the relatively large proportion of missing data.

8.2.0 RISK FACTORS ASSOCIATED WITH A SUBSEQUENT DIAGNOSIS OF INFLAMMATORY POLYARTHRITIS FOLLOWING PMR IN EPIC-NORFOLK

The rate of occurrence of inflammatory polyarthritis (IP) amongst participants diagnosed with PMR was calculated using Cox-proportional modelling with competing risk for death. At baseline, clinical features of those diagnosed with PMR were examined to determine whether there were differences between early or late transformations to IP, and to assess whether clinical features at presentation might predict those at risk of subsequent IP diagnosis. To assess how robust the findings were

to disease definition we repeated the analysis using classification criteria to define cases of PMR (35) and RA (226).

8.2.1 PMR cohort construction

From the 24,068 men and women recruited into EPIC-Norfolk, a total of 363 persons were diagnosed with PMR between 1st February 2002 and 31st January 2015.

There were 39 refuted diagnoses comprising osteoarthritis (n=13), rotator cuff tendinopathy (n=11), cervical spondylosis (n=6), malignancy (n=5), and one each of statin-related myalgia, greater trochanteric pain syndrome, systemic lupus erythematosus and primary hyperparathyroidism.

The final sample comprised 324 incident diagnoses of PMR (73.2% female) with 65% of diagnoses made exclusively by general practitioners. The mean age at diagnosis was 75.6 years. The maximum follow-up was 13 years (median 4.82 years). Baseline characteristics are shown in Table 6.9.

Within the PMR cohort there were 65 deaths during the follow-up period, four who had been diagnosed with IP of whom three met RA classification criteria.

8.2.2 Incidence of inflammatory polyarthritis following a diagnosis of PMR

During 1,855 person years of follow-up, 32 (10.5%) participants (20, 63% female) were diagnosed with IP by a rheumatologist (see Figure 6.4), nine diagnoses of IP were made within six months of diagnosis of PMR. The cumulative incidence, accounting for censoring for losses to follow-up and competing risk for death, of IP occurrence at six months, one, two, five and ten years was: 2.2% (95% CI 1.0 to 4.3), 3.5% (95% CI 1.9 to 6.0), 6.5% (4.1 to 9.6), 8.4% (5.6 to 11.9), and 12.9% (8.8 to 17.9) respectively. Using only those cases of PMR fulfilling the current ACR/EULAR resulted in a PMR cohort of 292 participants, of whom 26 developed IP, 12 of whom met the current criteria for RA. The subsequent cumulative rate for RA occurrence at six months, one, two, five and ten years was 1.1% (95% CI 0.3 to 2.9), 1.1% (95% CI 0.3 to 2.9), 1.8% (0.7 to 3.9), 4.0% (2.0 to 7.0), and 5.4% (2.9 to 9.1) respectively.

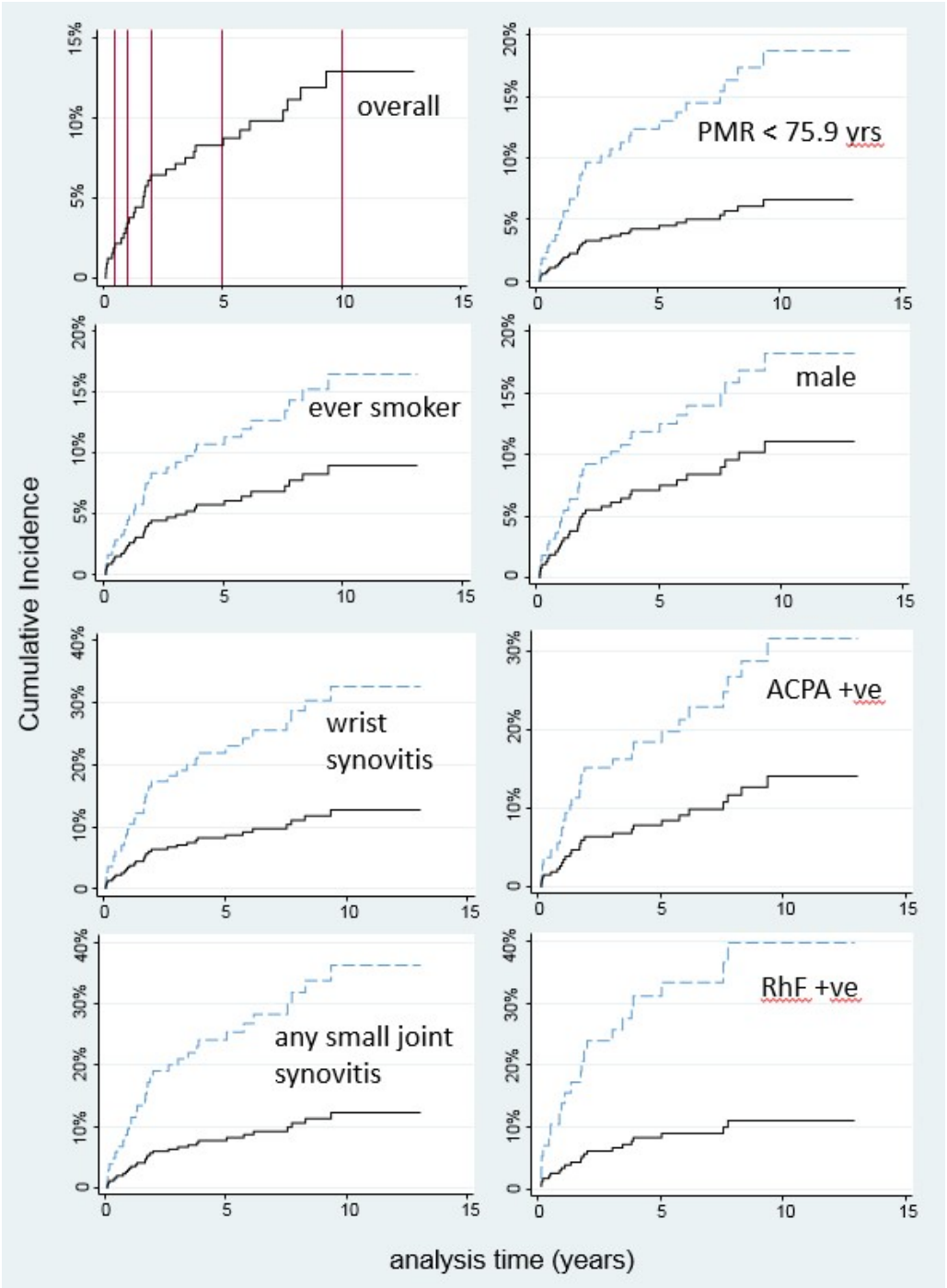
Clinical features remained broadly similar between those participants diagnosed with IP within six months, and the remaining IP cases, with the only difference found being a higher CRP at baseline PMR diagnosis (see Table 6.9).

Table 8.3 Baseline characteristics of those diagnosed with polymyalgia rheumatica

Population	Age at PMR diagnosis [a]	Female n (%)	Never smokers n (%)	ESR mm/hr (95% CI)[a]	CRP mg/L (95% CI) [a]	RhF positive	ACPA positive	Meeting EULAR/ACR PMR criteria	Any small joint synovitis
Total initial PMR diagnosis (n=363)	75.3	266 (73%)	163 (45%)	54 (51, 58)	43 (36, 50)	14/224 (6%)	26/258 (10%)	N/A	N/A
PMR cohort (n=324) [†]	75.6	237 (73%)	146 (46%)	56 (52, 60)	47 (39, 55)	12/203 (6%)	25/233 (11%)	292/324 (90%)	15/324 (5%)
Men (n=87)	76.1	N/A	60/87 (31%)***	52 (45, 59)	50 (37, 64)	5/50 (10%)	4/63 (6%)	79	6 (5%)
Women (n=237)	75.4	N/A	119/234 (51%)***	58 (53, 62)	46 (36, 56)	7/153 (5%)	21/170 (12%)	213	9 (3%)
Remaining as PMR (n=290)	75.9**	216 (75%)	135 (47%)	56 (52, 60)	47 (38, 56)	8/180 (4%)**	20/205 (10%)	264/290 (91%)	10 (4%)***
Transforming to IP (n=34)	72.8**	21 (62%)	11 (32%)	57 (43, 71)	51 (27, 75)	4/23 (17%)**	5/28 (18%)	28/34 (82%)	5 (15%)***
Early transformers (n=9)	76	4 (44%)	2 (22%)	71 (42, 101)	85 (31, 138)**	1/8 (13%)	1/7 (14%)	8/9 (89%)	2 (22%)
Late transformers (n=25)	71.6	17 (68%)	9 (36%)	51 (34, 67)	34 (10, 58)**	3/15 (20%)	4/21 (19%)	20/25 (80%)	3 (12%)

[†]For all PMR once the 39 whose diagnosis was refuted other than those considered to have IP. Early transformer are those being diagnosed with IP with 6 months of PMR diagnosis [a]students non-paired t-test, all other variables tested using chi^2 ** p value <0.05 *** p value <0.01

Figure 8.1 Cumulative incidence for IP in the PMR cohort by clinical feature with competing risk of death using Cox modelling



Cummulative incidence density using Cox-proportional hazard modelling with Fine-Gray extension for IP amongst participants diagnosed with PMR. Dashed lines refer to those participants with the risk factor present compare to the solid line – those without.

8.2.3 Clinical characteristics at baseline predictive of subsequent occurrence of IP

In the first five years males were at greater risk of IP compared to females (cumulative incidence for males at 1 and 5 years: 7.1% (2.9 to 13.8) and 13.1% (6.9 to 21.2); females: 2.2% (0.8 to 4.7) and 6.6% (3.8 to 10.5)), see Figure 6.1.

Table 6.10 shows clinical features and characteristics at baseline and their risk for subsequent IP occurrence using competing risk Cox regression analysis. Risk estimates were calculated for all PMR diagnoses; those fulfilling the classification set and those who were subsequently considered to have IP following clinical diagnosis, and those meeting the classification set for RA. Associated with the greatest hazard for subsequent diagnosis of IP or RA, irrespective of whether the cases of PMR fulfilled the current classification set for PMR, was small joint synovitis at time of PMR diagnosis. Rheumatoid factor carried a greater risk for subsequent IP and or RA compared to ACPA.

Table 8.4 Sub-hazard ratios for IP/RA by clinical features at baseline diagnosis of PMR using Cox modelling with competing risk of death

Clinical feature – all cases of PMR (n=324)	PMR changing to IP (n=32)	
	Sub-hazard ratio and 95% CI	p value
Age at time of PMR diagnosis >75.9 years	0.33 (0.15, 0.74)	0.007
Male sex	1.72 (0.84, 3.53)	0.139
Ever smoked	1.93 (0.92, 4.04)	0.083
adjusted	1.77 (0.84, 3.72)	0.131
RhF Positive	4.28 (1.48, 12.37)	0.007
adjusted	3.46 (0.89, 13.51)	0.074
ACPA Positive	2.51 (0.93, 6.72)	0.068
adjusted	3.14 (1.16, 8.54)	0.025
Wrist synovitis at time of PMR diagnosis	2.91 (0.40, 20.96)	0.290
adjusted	3.41 (0.54, 21.50)	0.192
Small joint synovitis at time of PMR diagnosis	3.45 (1.14, 10.42)	0.029
adjusted	3.11 (1.08, 8.93)	0.035
Cases of PMR meeting EULAR/ACR criteria* (n=292)	**PMR changing to RA (n=12)**	
	Sub-hazard ratio and 95% CI	**p value**
Age at time of PMR diagnosis >75.9 years	0.49 (0.15, 1.62)	0.244
Male sex	1.47 (0.45, 4.84)	0.524
Ever smoked	1.83 (0.56, 5.95)	0.317
adjusted	1.72 (0.50, 5.93)	0.393
Wrist synovitis at time of PMR diagnosis	7.66 (0.93, 62.93)	0.058
adjusted	8.55 (1.05, 69.74)	0.045
Small joint synovitis at time of PMR diagnosis	6.69 (1.44, 31.13)	0.015
adjusted	6.17 (1.34, 28.43)	0.019

Clinical features at baseline at time of PMR diagnosis and subsequent risk of IP or RA occurrence using Cox hazard modelling with competing risk for death. *The EULAR/ACR criteria for PMR include a requirement for lack of rheumatoid factor and or anti-ccp antibodies.

In those younger at PMR onset there was a greater risk of IP. The majority of participants with IP were rheumatoid factor negative (81.8%), one of whom was positive for ACPA. During the follow-up period 12/20 (60.0%) women and 4/12 (33.3%) men fulfilled the EULAR ACR criteria set for rheumatoid arthritis (see Table 2). Of the participants with IP, five developed erosions (15.6%) during the follow-up period, of whom three (18.8%) fulfilled the current RA classification set. The presence of peripheral synovitis at baseline diagnosis was noted in 13 (4.5%) of those considered subsequently to remain as PMR, three (9.4%) of those considered subsequently to have IP and two (12.5%) of those considered subsequently to have RA. The positive likelihood ratio for peripheral synovitis at baseline PMR diagnosis was 2.1 for IP and 2.7 for RA, this ratio increasing if only those who fulfilled the current classification criteria for PMR were used for the baseline cohort, resulting in positive likelihood ratios of 2.3 and 3.3 for IP and RA respectively.

8.2.4 Comments

Although the number of participants who developed IP was relatively small, the detailed characterisation of the PMR cohort and the ability to apply current classification criteria were major strengths of this analysis. From the data available from the EPIC-Norfolk cohort, males and those who smoked were at greatest risk of subsequent IP diagnosis.

8.3.0 CONCLUSIONS OF RISK FACTORS FOR PROGRESSION

These are the first estimates for onset of PMR and GCA from a prospective cohort study. Whilst challenges exist in applying classification criteria retrospectively, the ability to define cases which meet classification criteria is a major strength of this work.

8.3.1 Risk factors for blindness in GCA

The DCVAS analysis indicates that blindness is still a major concern with a diagnosis of GCA and most individuals who had visual disturbance at presentation were declared blind at six months of follow-up. Whilst the definition of blindness is severe in terms of the spectrum of visual loss, it is a robust measure and compares similarly to results from the Mayo clinic, with 14.9% of patients in their series suffering monocular blindness (136).

8.3.2 Risk factors for inflammatory arthritis following a diagnosis of PMR

There is significant overlap in the clinical features of PMR, IP and RA, and due to lack of a single diagnostic test with which to separate them, makes studying these sub-populations difficult. However, every attempt was made to start with a pure PMR cohort. We excluded all diagnoses other than for IP which occurred in our PMR participants within six months from original PMR diagnosis. As a single clinical feature, the use

of peripheral joint synovitis to differentiate between PMR and IP is inappropriate, with many other authors concluding that such a finding is a feature of PMR. In addition, there are many cases of IP and indeed RA which lack serology from RhF and ACPA yet the lack of these markers does not prevent the individual from developing inflammatory arthritis. While, in keeping with many others on this subject, this study relied on a single rheumatology unit for its diagnoses of RA (227-229), this unit is the largest in the region and catchment area for the EPIC-Norfolk population with its patients contributing to the long-running inflammatory arthritis data for the Norfolk Arthritis Register (NOAR) (230).

CHAPTER 9 OCULAR MORPHOMETRY – RETINAL CHANGES AND CHARACTERISTICS

9.0 SUMMARY

Retinal images were acquired from participants who attended the third health check, known as the EPIC-Eye study, the dates of which were from 2005 to 2011. Non-mydratic digital retinal images were captured using a Topcon fundus camera. Images were reviewed for retinal characteristics to ascertain whether any morphological features were associated with cases of PMR or GCA compared to controls. Digital retinal images were reviewed at Moorfield eye hospital with independent review by technicians. Features were recorded using the scoring sheet in Appendix 2. The aim was to establish whether any morphological features were characteristic of either PMR or GCA compared to matched controls.

9.1.0 Data Source EPIC-Eye

In total there were 135 cases of PMR and / or GCA, these comprising 103 cases of PMR, and 32 cases of GCA, of whom nine had co-existing PMR with GCA.

The results of the inflammatory marker assessment at time of diagnosis were similar to all cases at diagnosis from the cohort – See Table 5.5. Previously published studies had found an association between lower inflammatory markers at baseline and increased risk for visual loss in

patients with GCA (see Section 2.6.7). The cases for the EPIC-Eye study had ESR measured at time of diagnosis:

- PMR cases ESR (mm/hr): mean 51 (SD 27), median 46 (IQR 38);
- GCA cases ESR (mm/hr): mean 82 (SD 36), median 91 (IQR 54);
- Co-existing cases ESR (mm/hr): mean 62 (SD 33), median 52 (IQR 61).

The dates of diagnosis ranged from 1st Jan 1984 to 9th June 2015, with the date ranges for the third health check 17th August 2005 to 28th October 2011. This resulted in 56 (41.5%) individuals having their retinal fundus photograph taken before their diagnosis of PMR and / or GCA. The visual acuity of those participants who attended the third health check is described in Chapter 5.3.2.

9.2.0 RETINAL FIELD CHARACTERISTICS

The QUARTZ processed images have showed an increase in retinal venule width amongst participants with PMR. The images were reviewed to record other changes affecting the retinal field including a focal narrowing not captured by QUARTZ.

Retinal characteristics were reviewed, from digital retinal images, independently by two researchers documenting features such as, focal vascular changes, disc morphology and retinal field characteristics. This comprised case-control analysis using the 17 incident cases of GCA and

39 cases of PMR, age and sex matched to three controls per case (n=168). A third senior researcher reviewed any discrepancies and made the final over-riding decision on the presence or absence of any characteristics (as described in methods chapter 4.3.6 and 4.3.7). In addition a selection of prevalent cases (those being diagnosed with PMR or GCA prior to health check three) were reviewed (PMR n = 64 and GCA n = 15) in order to ascertain whether the characteristics were present before or as a consequence of a diagnosis of PMR or GCA. Table 8.3 gives the disease status of all 303 participants reviewed for retinal field characteristics.

Table 9.1 Cases of PMR and GCA by incident or prevalent disease status

Diagnosis	Number	Incident cases n = 56	Prevalent cases n = 79
PMR	103	39	64
GCA	32	17	15
Controls*	168	N/A	N/A

*controls matched on sex and age at time of retinal photograph to the incident cases (ratio 3:1).

All retinal images were independently scored by two assessors. Any disagreements were highlighted with a third reader having final say on final scoring. Retinal field characteristics were recorded, including focal narrowing, arteriovenous nipping (AV nipping), pigment field loss, tigroid fundus and disc morphology. In total 38 cases were adjudicated by the

third reviewer. The retinal morphology characteristics presented are the final adjudicated set.

9.2.1 Tigroid Fundus

Potentially tigroid or tessellation of the fundus could have be as a consequence of disease or due to ageing. Table 8.4 details the prevalence of tigroid fundus by disease status.

Table 9.2 Tigroid Fundus

Diagnosis	Number	Strong n (%)	Mild n (%)	None n (%)
Prevalent PMR (n=64)	52	16 (30.8)	17 (32.7)	19 (36.5)
Incident PMR (n=39)	32	11 (34.4)	13 (40.6)	8 (25.0)
Prevalent GCA (n=15)	13	6 (46.2)	5 (38.5)	2 (15.4)
Incident GCA (n=17)	14	4 (28.6)	7 (50.0)	3 (21.4)
Control (n=168)	136	63 (46.3)	51 (37.5)	22 (16.2)

Chi2 test p = 0.162 with Fisher's exact p = 0.179.

The analysis shows the presence of tessellation is not associated with cases of GCA and or PMR prior to or after their diagnosis. The cases were diagnosed between 28 days and 8.3 years from their third health check date. The median time period between the third health check and diagnosis was 2.9 years with 75% of cases having an interval of at least one year.

9.2.2 Focal vessel narrowing and arteriovenous nipping

Review of the images revealed only focal narrowing of vessels in the superior nasal quadrant. In total only five participants were noted to have possible focal narrowing in the left eye, four with PMR (two with incident disease) and one control.

AV nipping was noted in a number of participants. There was good agreement when no AV nipping was thought to be present (78 participants vs 93 participants with agreement on 75 participants between first and second readers). However when changes were noted, there were discrepancies: the first reader noted possible changes of AV nipping in three participants with the second reader noting changes in one participant not observed by the other reader. The biggest difference was noted in those thought to have definite changes. A third reader reviewed the cases where there were discrepancies and the final adjudicated features were noted (See Table 8.5).

There appeared to be no good statistical evidence to suggest there were any major differences between the cases and controls in respect of the presence of AV nipping. The total prevalence of AV nipping if present in any quadrant of either left or right eye was as follows: prevalent PMR 18.8%, incident PMR 15.4%, prevalent GCA 20.0%, incident GCA 17.7% and controls 13.7%. Combining all the incident cases of PMR and GCA and comparing them with their age and sex controls resulted in a prevalence of AV nipping for the cases of 16.1% vs 13.7% for the

controls, but this difference was not statistically different with a chi^2 of 0.659.

Table 9.3 Arteriovenous nipping by quadrant and left or right eye

Cases	Superior nasal quadrant		Inferior nasal quadrant		Superior temporal quadrant		Inferior temporal quadrant	
	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye
Prevalent PMR (n=64)	6 (14.3)	7 (16.7)	3 (7.3)	4 (9.3)	1 (2.4)	0	1 (2.5)	2 (4.9)
Incident PMR (n=39)	2 (6.7)	2 (6.9)	1 (3.5)	3 (10.3)	2 (6.9)	1 (3.5)	0	3 (10.3)
Prevalent GCA (n=15)	1 (12.5)	0	2 (25.0)	1 (11.1)	0	0	0	1 (12.5)
Incident GCA (n=17)	1 (10)	2 (15.4)	0	0	0	0	0	0
Control (n=168)	9 (12.3)	6 (8.0)	3 (4.1)	6 (7.9)	2 (2.7)	0	0	1 (1.4)

No statistical significant difference between disease status by each quadrant of each eye using Fisher's exact test.

Table 9.4 Retinal pigment epithelium loss

Cases	Superior nasal quadrant		Inferior nasal quadrant		Superior temporal quadrant		Inferior temporal quadrant	
	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye
Prevalent PMR (n=64)	2 (4.4)	4 (9.0)	9 (19.6)	9 (19.6)	1 (2.3)	1 (2.2)	2 (4.7)	1 (2.5)
Incident PMR (n=39)	1 (3.3)	0	6 (20.0)	6 (19.4)	0	0	1 (3.5)	1 (3.5)
Prevalent GCA (n=15)	1 (14.3)	1 (10.0)	1 (14.3)	1 (10.0)	1 (16.7)	1 (12.5)	0	0
Incident GCA (n=17)	0	0	2 (16.7)	4 (25.0)	0	0	0	1 (8.3)
Control (n=168)	2 (2.7)	4 (5.4)	10 (13.5)	16 (21.9)	1 (1.4)	1 (1.4)	2 (2.7)	1 (1.4)

No statistical significant difference between disease status by each quadrant of each eye using Fisher's exact test.

For patches of loss of retinal epithelial pigment (REP) there was good agreement between the first and second readers particularly when no loss was thought to be present (80 vs 83 participants thought to have no loss of REP – agreement on 72 of the participants). Again a third reader was used to arbitrate on any discrepancies. There appeared to be no good statistical evidence to suggest there were any major differences between the cases and controls in respect of the presence of REP loss.

9.2.3 Optic disc morphology

GCA is known to cause anterior ischaemic optic neuropathy, typically in the hyper-acute phase of the illness and visual symptoms may be the first symptom of GCA at presentation. Unfortunately around one in 12 people diagnosed with GCA will suffer blindness in the affected eye. Initially the disc can look swollen and / or pale but typically these changes resolve within a few weeks. Where ischaemia has been prolonged, the disc can atrophy and appear chalky white. Since other changes may be noted with the disc, discs from the EPIC-participants with retinal images were recorded. The results are below in Table 8.7.

Table 9.5 Optic disc morphology

		Optic disc morphology							
		Normal	**Atrophy**	**Pale**	**Cupping**	**Laminar dot sign**	**Thick NNR**	**Blurred nasal edge**	**Blurred temporal edge**
Prevalent PMR (n=64)	**right eye** (n=63)	18 (28.6)	0	4 (6.4)	2 (3.2)	5 (7.9)	26 (41.3)	2 (3.2)	6 (9.5)
	left eye (n=60)	19 (31.2)	1 (1.7)	5 (8.3)	2 (3.3)	4 (6.7)	20 (33.3)	0	9 (15.0)
Incident PMR (n=39)	**right eye** (n=38)	14 (36.8)	0	0	0	2 (5.3)	16 (42.1)	1 (2.6)	5 (13.2)
	left eye (n=38)	15 (39.5)	0	1 (2.6)	0	2 (5.3)	15 (39.5)	1 (2.6)	4 (10.5)
Prevalent GCA (n=15)	**right eye** (n=15)	8 (53.3)	0	0	0	0	6 (40.0)	0	1 (6.7)
	left eye (n=15)	11 (73.3)	0	1	0	0	3 (20.0)	0	0
Incident GCA (n=17)	**right eye** (n=17)	10 (58.8)	0	0	0	1 (5.9)	6 (35.3)	0	0
	left eye (n=17)	8 (47.1)	0	0	0	1 (5.9)	6 (35.3)	0	2 (11.8)
Control (n=168)	**right eye** (n=87)	55 (63.2)	0	0	4 (4.6)	13 (14.9)	9 (10.3)	0	3 (3.5)
	left eye (n=77)	43 (55.8)	0	0	2 (2.6)	12 (15.6)	17 (22.1)	0	3 (3.9)

*thick neuroretinal rim (NRR) / small cup – disc to cup ratio of 0.25 or less.

9.2.4 Peripapillary atrophy (PPA)

The digital retinal images were also reviewed for the presence of peripapillary atrophy. There was good agreement between the first and second readers with an agreement of 94.0% for the left eye and 92.5% for the right eye and 96.1% between eyes with a weighted kappa statistic of 0.75. The arbitrated features of PPA are shown in Table 8.8.

Table 9.6 Peripapillary atrophy

		Peripapillary atrophy			
Participant group		**None**	**temporal**	**Nasal**	**Circumferential**
Prevalent PMR (n=64)	**right eye** (n=58)	47 (81.0)	7 (12.1)	1 (1.7)	3 (5.2)
	left eye (n=53)	40 (75.5)	7 (13.2)	2 (3.8)	4 (7.6)
Incident PMR (n=39)	**right eye** (n=33)	25 (75.8)	8 (24.2)	0	0
	left eye (n=34)	25 (73.5)	8 (23.5)	0	1 (2.9)
Prevalent GCA (n=15)	**right eye** (n=14)	13 (92.9)	1 (7.1)	0	0
	left eye (n=15)	12 (80.0)	2 (13.3)	0	1 (6.7)
Incident GCA (n=17)	**right eye** (n=17)	17 (100.0)	0	0	0
	left eye (n=15)	15 (100.0)	0	0	0
Control (n=168)	**right eye** (n=84)	61 (72.6)	8 (9.5)	5 (6.0)	10 (11.9)
	left eye (n=74)	59 (79.7)	9 (12.2)	4 (5.4)	2 (2.7)

9.2.5 Other changes

Other characteristics were also recorded, including: the presence of drusen, age related macular degeneration, epiretinal membrane (ERM), myopic atrophy and age-related macular degeneration (AMD), with descriptions recorded are shown in Table 8.9. None of the field changes were associated with cases of PMR and / or GCA more than for controls.

Table 9.7 Other characteristics of retina

Characteristic	PMR (n=103)	GCA (n=32)	Controls (n=168)
No changes recorded	90 (87.3%)	28 (87.5%)	147 (87.5%)
Drusen	5 (4.9%)	3 (9.4%)	8 (3.0%)
ERM	1 (1%)	0	2 (1.2%)
Myopic atrophy	1 (1%)	0	0
AMD	0	1 (3.1%)	0

ERM - Epiretinal membrane, AMD – Age related macular degeneration.

9.2.6 Comments

Following careful and thorough review of 303 participants with digital retinal images, no characteristic features were displayed for either participants with PMR or GCA. The lack of any characteristic features amongst participants with GCA may due to the relatively small number reviewed.

9.3.0 CONCLUSIONS OF RETINAL MORPHOMETRY IN PMR AND GCA

This is the first time a thorough review of retinal morphology has been carried out amongst patients with PMR and GCA and compared to age and sex-matched controls. There were between 13.7% and 20.0% of participants showed AV nipping, compared with 18.7 to 20.3% on anti-hypertensive therapy at baseline. Further analysis is required to ascertain the validity of the various definitions of hypertension and subsequent

development of AV nipping, but this work remains beyond the scope of this thesis

The use of automated software enables reliable processing of the images in a relatively quick time-frame. However, in order to allow efficient processing, the QUARTZ program removes any areas where there is cross-over of retinal vessels and therefore information on arteriovenous nipping is not captured. The QUARTZ program produces vasculometric measures of retinal vessel width for arteriole and venules which may be important in disease development or risk, with changes in vessel calibre associated with cardiovascular risk factors.

CHAPTER 10 OCULAR SCREENING - QUARTZ

10.0 SUMMARY

The above chapter above describes the recording and cataloguing of retinal characteristics using automated software and manual review. The QUARTZ program produces measures of vessel width at the pixel level, with analysis of retinal width being carried out using a standardised measure of vessel width for the whole retina captured in the image. This process has been shown to be reliable and has been validated using both EPIC-Norfolk and UK Biobank images.

10.1.0 RETINAL VASCULAR MORPHOLOGY – VESSEL WIDTHS

Retinal fundal images were assessed in collaboration with researchers at St George's Hospital, University of London. This group have developed QUARTZ (QUantitative Analysis of Retinal Vessel Topology and siZe), a software system providing automated quantification of retinal vessel morphology (Chapter 4.5.3 for detailed methods of the QUARTZ program).

Retinal vessel tortuosity is associated with a number of established cardiovascular risk markers in the first decade of life (231). This suggests life-course patterning of vascular development and that retinal vessel morphology may be an important early marker of vascular health. Hence, accurate assessment of retinal vessel morphology (in both arterioles and

venules) may be an important biomarker of vascular health, which may predict those at high risk of disease in middle and later life.

Using a case-control design retinal vascular morphology changes associated in patients with GCA or PMR are reported.

10.1.1 Measures of retinal vessel width

Retinal vessel width measures were calculated for all participants who attended the third health check and had digital retinal images which could be processed by the QUARTZ program (232). The retinal vessels are classified into venules and arterioles and a mean summary measure for venules and arterioles calculated for each participant. Average width measures for arterioles and venules for each eye is calculated. Data presented are based on Gaussian modelling for vessel widths and an ensemble classifier of bagged decision trees using colour information for the vessel type (arteriolar vs venular retinal vessel – not choroid vessels). Only vessels with a high degree of certainty (probability >75%) of the correct vessel type being awarded by the classifier were used.

10.1.2. Retinal vascular widths

In total, 10,494 images of adequate quality were obtained and analysed from 5,959 participants. Of these participants, 5,125 had images of adequate quality from both right and left eyes. Mean arteriolar and

venular widths were 64.8 µm (SD 8.4), and 93.6 µm (SD 10.1) respectively.

Of those who attended the third health check with retinal images which could be processed by the QUARTZ program, there were 132 participants with PMR and 42 with GCA. Of these cases, 49 of the participants with PMR and 23 of those with GCA were diagnosed after attending their third health check. The mean age of those with PMR at health check three was 75.3 years (SD 7.6) and for those with GCA the mean age was 72.8 years (SD 7.9). The mean ESR at diagnosis was 56 mm/hr for those with PMR and 74 mm/hr for those with GCA (See Table 9.1 for baseline characteristics).

Table 10.1 Baseline Characteristics of all participants attending the third health check

	PMR (n = 132)	GCA (n = 42)	Control (n = 7,938)
mean (SD) age at hc3, years	75.3 (7.6)	72.8 (7.9)	68.7 (8.1)
Female sex (%)	93 (70.4%)	30 (71.4%)	4,373 (55.1%)
Never smokers (%)	49.60%	46.30%	52.40%
mean (SD) arteriolar width, µm	65.0 (9.6)	65 (7.5)	64.8 (8.4)
mean (SD) venular width, µm	97.6 (10.9)	92.8 (8.4)	93.6 (10.1)

The above calculations include all those with a diagnosis of GCA or PMR irrespective of the date of their third health check.

Of the 72 cases with QUARTZ analysed images prior to their diagnosis of PMR and / or GCA, 56 (77.8%) participants had retinal fundal images

available for manual review to assess for retinal morphology characteristics. For the retinal morphology work, these cases (n=56) were age and sex matched to three controls (n=168). Features associated with subsequent diagnosis of PMR and / or GCA were analysed.

Participants with PMR had wider venular widths compared to those without (mean difference 4.0 μm, 95% CI 1.7, 6.3 μm); there were negligible differences in arteriolar diameter (mean difference -0.2 μm, 95% CI -1.8, 2.3 μm). There were no appreciable associations between vessel width and GCA. The difference in retinal venular widths was present in cases prior to their diagnosis of PMR. Adjusting for age and sex using multi-linear regression did not nullify the results (See Table 8.2).

10.1.3 Sensitivity analysis and retinal vessel widths

The linear regression model was recalculated using only those cases meeting the ACR criteria set for GCA and only those meeting the EULAR-ACR criteria set for PMR. This resulted in no overall changes in the estimates (data not shown).

Table 10.2 Vessel width for incident and prevalent cases of PMR and GCA

	Total	Incident cases	Prevalent case	Control n=7,938
PMR (n)	132	49	83	
Venular width (μm) and SD[b]	97.6 SD 10.9	98.9 SD 13.3	96.5 SD 8.6	93.6 (SD) 10.1 from 5,033 controls
Δ Venular width (μm) 75% probability*	4.0 (1.7, 6.3) p=0.001	5.4 (0.7, 10.1) p=0.003	3.0 (0.5, 5.5) p=0.06	Reference
Regression co-efficient for venular width†	3.96 (1.57, 6.35) p=0.001	5.43 (1.79, 9.06) p=0.003	2.86 (-0.29, 6.0) p=0.075	N/A
Arteriolar width (μm) and SD[b]	65.0 SD 9.6	65.5 SD 11.3	64.7 SD 8.2	64.8 (SD) 8.4 from 5,034 controls
Δ Arteriolar width (μm) 75% probability*	-0.2 (-1.8, 2.3) p=0.8231	0.7 (-3.3, 4.7) p=0.648	-0.1 (-2.5, 2.7) p=0.924	Reference
Regression co-efficient for arteriolar width†	0.69 (-1.29, 2.68) p=0.495	1.09 (-1.94, 4.13) p=0.479	0.42 (-2.18, 3.01) p=0.754	N/A
GCA (n)	42	23	19	
Venular width (μm) and SD[b]	92.8 SD 8.4	93.7 SD 8.9	90.4 SD 6.9	93.6 (SD) 10.1 from 5,033 controls
Δ Venular width (μm) 75% probability*	-0.8 (-4.2, 2.7) p=0.730	0.2 (-4.3, 4.6) p=0.951	-3.2 (-10.1, 3.8) p=0.446	Reference
Regression co-efficient for venular width †	-0.59 (-4.82, 3.6) p=0.785	0.33 (-4.63, 5.28) p=0.897	-3.02 (-11.10, 5.06) p=0.464	N/A
Arteriolar width (μm) and SD[b]	65.0 SD 7.5	66.0 SD 8.1	62.2 SD	64.8 (SD) 8.4 from 5,034 controls
Δ Arteriolar width (μm) 75% probability*	-0.2 (-2.9, 3.3) p=0.918	1.2 (-2.9, 5.3) p=0.565	-2.6 (-7.9, 2.7) p=0.457	Reference
Regression co-efficient for arteriolar width †	0.58 (-2.94, 4.11) p=0.745	1.56 (-2.57, 5.70) p=0.458	-2.03 (-8.77, 4.71) p=0.554	N/A

Δ mean difference between cases and controls. Controls comprise 7,938 participants unless otherwise stated. [b]two-sample non-paired t-test between incident and prevalent cases as respect of third health check and venular width and arteriolar width respectively for PMR and GCA cases revealed p=>0.1. * two-sample non-paired t-test between cases and controls for all cases, incident cases and prevalent cases respectively † Linear regression on venular width with presentation of regression co-efficient and adjusting for age at the time of retinal photograph and sex of the participant.

10.1.4 Comments

The self-selected participants, with PMR or GCA attending the third health check did not differ in their gender or age at diagnosis compared to the rest of the cohort who had been diagnosed with PMR and GCA. The inflammatory markers at time of diagnosis were also similar. Nonetheless, the participants who attended the third health check could potentially result in a biased sample towards those with good vision as those with poor vision may have found travelling for assessment more burdensome.

The presence of increased retinal venular width in cases with PMR is of interest and is plausibly related to vascular dysfunction. It is noteworthy that the increase in venular width was present prior to their diagnosis of PMR. The lack of any association between retinal vessel measures and GCA could be due to small numbers, or there may be no difference in retinal vessel widths between cases and controls.

10.2.0 EXPLORATORY ANALYSIS

However, each image processed by QUARTZ provides thousands of data points recorded within a large data and this additional data might be useful in further research.

The approach to the data file could take two broad approaches

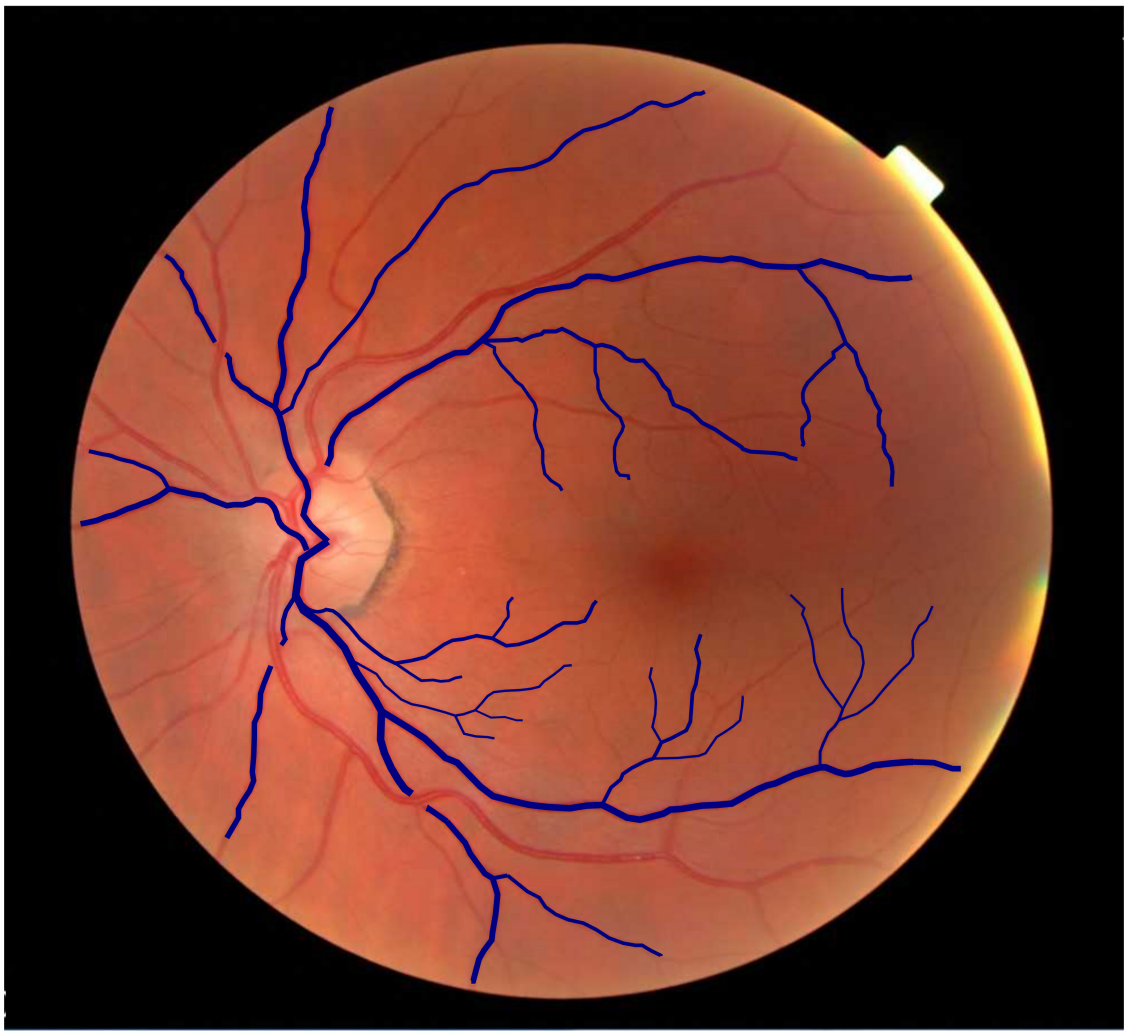
Data driven - looking at the output how many clusters explain the variance in the data?

Goal driven - are there specific features we would hope to find based on the data of width, length and tortuosity?

The data can look at the width, the length, the branching pattern, and how these are linked together in what is known as the “network”.

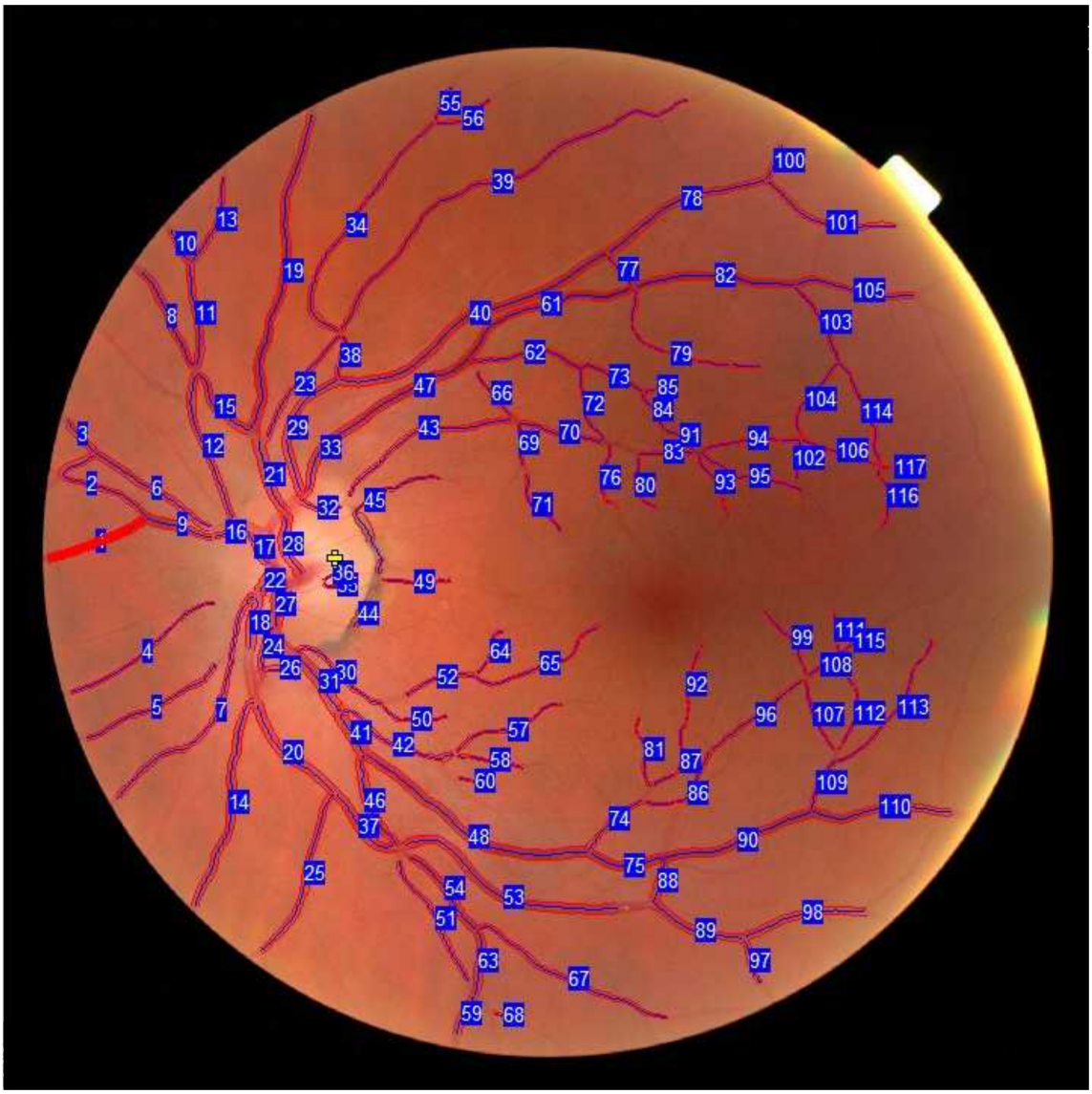
The data file for one eye was obtained and the corresponding digital retinal image is shown in Figure 9.1. and Figure 9.2 shows the labelled segments once the image has been processed by QUARTZ.

Figure 10.1 Digital retinal image



Digital retinal fundus image of a left eye from an EPIC-Norfolk participant. The venules in this image have been coloured in blue to facilitate discrimination between venules and arterioles.

Figure 10.2 QUARTZ labelled retinal image



Segmented vessels after processing by QUARTZ. Segment 44 is an artifact.

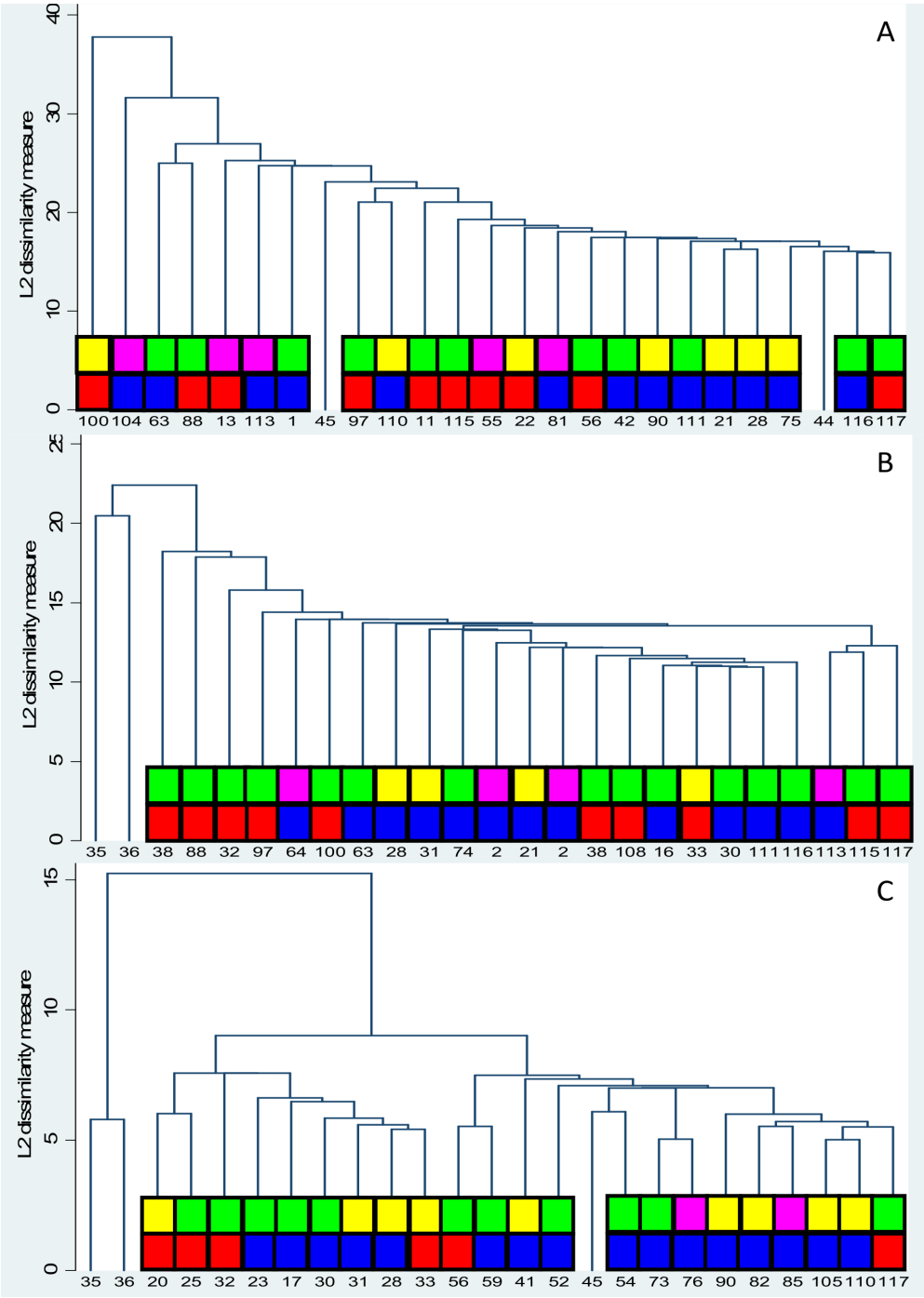
10.2.1 Cluster analysis

Cluster analysis was taken of a processed QUARTZ image to see if the vessel segments grouped together. The variables used in the model were vessel width, local angle and location of the measures on the image. The

QUARTZ program records the orientation of the centre line (based in the central reflex of the vessel – see chapter 4.3.4 for details).

Cluster analysis was performed, creating a location variable based on the x and y coordinates. This was carried out firstly with an origin in the top left corner and secondly with the origin set as the optic disc. Cluster analysis was undertaken including segment vessel width, local angle and location origin with subsequent dendrograms produced labelled by segmentation number (see Figure 9.3). The diagram shows the results of three cluster analysis models: A is a dendrogram based on a cluster model comprising an origin in the top left corner, vessel segment width, and local angle, B is a dendrogram based on a cluster model comprising an origin of the optic disc, vessel segment width and local angle and C is a dendrogram based on a cluster model comprising an origin of the optic disc and vessel segment width.

Figure 10.3 Dendrograms following Cluster analysis



Dendrograms for the various cluster analysis models. Key for coloured boxes: yellow 1st, green 2nd, and purple 3rd order vessels, red arterioles, blue venules. Segments 35, 36 and 45 comprise small vessels on or arising from the disc which are impossible to categorise, segment 44 is an artefact.

10.2.2 Comments

The results of the cluster analysis and subsequent dendrograms are shown in Figure 9.3. The models using the optic disc as the origin appear to group venules and arteriole segments better than the model with the origin set as the top left corner. There were many leaves in the cluster analysis and so an arbitrary cut of 25 levels was chosen. The results don't show a strong separation by vessel segment, type, and location from the optic disc. Further work is needed to ascertain if more information can be used from the QUARTZ output but remains beyond the scope of this thesis.

CHAPTER 11 DISCUSSION

11.0 SUMMARY

This chapter concludes by considering how far the work presented in this thesis has been able to address its stated aims. Limitations in the study design and set-up of the three main dataset are given including which inherent biases could influence the results and subsequent conclusions. The chapter finishes by considering how the questions and problems highlighted could be addressed by intended further work.

11.1.0 GCANS - strengths

Previous studies of PMR and GCA have been criticised as they often recruit participants from secondary care populations and therefore are unrepresentative of the underlying larger community population. The studies which have made use of community-based registries have often failed to apply classification criteria, making comparisons difficult. The GCANS study therefore aimed to address these criticisms by surveying a community population. However, there are limitations to this study.

Although the estimates from GCANS only apply to those individuals aged ≥55 years, within the sample only 5% of GP-recorded cases of PMR and no cases of GCA were diagnosed before this age. Although a large population, (in excess of 5000 people) were screened, the community is typical of rural Norfolk comprising a largely Caucasian population and an

older age demographic compared with the rest of the UK. Those aged > 55 years make up 36% of the Norfolk population compared with 29% for England and Wales so the older age of the Norfolk population it is likely to result in greater disease burden for PMR and GCA, since both conditions are strongly correlated to age with incidence density rising with each increase in age band. However, this region has provided epidemiological data on inflammatory arthritis and systemic vasculitis from the Norfolk Arthritis Register (NOAR) and Norfolk Vasculitis (NORVASC) cohorts (233, 234).

Through direct record review and questionnaire sampling supplemented by clinical assessment, considerable effort was made to enrich the available clinical data. While laboratory data were available in all cases of GP-recorded GCA, the results of tests of inflammatory makers were missing in the clinical records of 15% of those assigned a GP diagnosis of PMR. Incomplete GP records and where blood test results prior to the year 2000 could not be retrieved electronically prevented confirming a diagnosis of PMR. Confining the analysis to those individuals who responded to the questionnaire, the resulting prevalence estimates for GCA would be 0.19% (95% CI 0.07% to 0.32%) and 1.54% (95% 1.19% to 1.90%) for PMR.

No validated questionnaire exists for diagnosis or classification of either PMR or GCA. A concern was that cases might exist in the community which had not been identified by their GP. In the 1985 study by *Kyle et*

al., identified one case of GCA unknown to their GP. Historical diagnoses are difficult to capture through questionnaires, particularly in diseases that remit with treatment. It may have been difficult in this study to detect cases which had entered remission before 2000 who were also not captured on the GP records. However, by use of the combined approaches for case ascertainment, it is unlikely that undiagnosed or remitted disease were missed in this study. The results suggest that GP-recorded diagnoses are likely to encompass all cases within a population, although not all will fulfil classification criteria sets.

11.1.1 EPIC-Norfolk - strengths

The major strengths of the EPIC-Norfolk cohort are its large size, long duration of follow-up and depth of clinical data available. These allow the description of a rich phenotype of the diseases of interest and for application of classification criteria. In addition the prospective nature of its design negates the problems of recall bias inherent in case-control studies. In addition, reverse causality is minimised in prospective study designs because eventual cases are disease free at the start of follow-up and drawn from the same population as controls (235).

The estimates for disease incidence of both PMR, GCA, and their complications from this large community-based cohort provide advantages over other published estimates, namely the representativeness of the controls and the ability to apply classification sets of disease. The estimates of disease incidence are similar to other

published data suggesting these findings are valid. In keeping with the results for GCANS not all cases of PMR and GCA meet their intended classification criteria set.

The data on morbidity associated with PMR and GCA should also be interpreted with the knowledge that a full comprehensive visual assessment was made of those participants who attend the third health check. This is the first study of its kind to include detailed documentation of visual performance in such a large population and the use of digital retinal fundal images provides further insights into the disease aetiology of these important conditions.

Cardiovascular and other risk factors for onset were assessed using the EPIC-Norfolk cohort, again due to the careful review of potential cases and enriching the dataset with detailed phenotypic information is a major strength of this work. Whilst data on risk factors was collected at the baseline assessment, this data was recorded at nurse-led clinics and any associations found are unlikely to be biased upwards since participants within the cohort are likely to have developed hypertension subsequently and prescribed lipid lowering medication or anti-hypertensive agents.

Another major strength of the work is from the EPIC-Eye study in which over 8000 individuals had measurement of visual acuity and retinal fundal images were captured. This has allowed for estimates of the effect of a diagnosis of PMR and GCA has on visual performance and for calculation of both relative and absolute risks of visual impairment.

The other major part of the work on risk factors for progression was the development of IP in participants initially diagnosed with PMR. The shared clinical features between PMR and inflammatory polyarthritis are a diagnostic challenge for clinicians. Tracking the onset of PMR in the community setting is difficult, requiring adequate methods of disease classification and prolonged follow-up. Previous secondary care-based studies assessing the development of IP in patients with PMR have been published. In one, 21 (11.1%) patients with PMR developed arthritis during follow-up but it is unclear how many of these subsequently had their diagnosis changed to inflammatory polyarthritis and which of these fulfilled classification sets for RA (205). Other studies have reported that as many as 20% patients initially diagnosed with PMR go on to develop RA after twelve months of follow-up (17). No studies have found any clinical features consistently which would be of strong positive predictive value in identifying those who may be at increased risk of subsequent inflammatory polyarthritis (17).

Finally this is the first time a thorough review of retinal morphology has been carried out amongst patients with PMR and GCA and compared to age and sex-matched controls. Although no characteristics particular to PMR and GCA were found on manual review, the retinal vasculometric measures from the QUARTZ analysis are interesting and support a role for vascular dysfunction in the aetiology of PMR.

11.1.2 DCVAS - strengths

A strength of this study is its size: 433 new cases of GCA were included, each of which having a systematic structured assessment that included presenting features, comorbidities, and outcome at six months. Outcomes were assessed by the VDI, a validated means of recording permanent damage arising from vasculitis or its treatment.

This large observational study demonstrates that blindness remains a major problem in GCA: by six months after diagnosis, around one in twelve patients is blind in one eye. Although most patients who develop blindness do so by the time of their first assessment, two patients without symptoms of visual disturbance suffered blindness at six months. These results re-emphasise the need for urgent referral and rapid treatment with glucocorticoids (236). The analysis shows an association between blindness and peripheral vascular disease. Recently published data from the Swedish registry may be supportive of this evidence to suggest a possible aetiological role of vascular dysfunction as risk of blindness was greatest in individuals treated with beta-blockers (200).

The present study identified a lower rate of blindness than the majority of published estimates, possibly reflecting our narrower and more stringent definition of blindness. It could be that more patients in DCVAS suffered visual loss since 70 patients were noted to have this complication at their baseline visit. However, the Mayo clinic published data on 204 cases of GCA from Rochester, Minnesota, USA over a 55-year period revealing

patients (23.0%) had visual symptoms, with seven (3.4%) suffering blindness in one eye (of whom two had bilateral blindness), which is lower than our estimate (136). Subsequently this same research group reported that 8.2% of patients with GCA had permanent visual loss attributed to their vasculitis which newer data are more consistent with our current estimate (237). Our estimate is higher than the 2.9% reported in the register-based study by Mollan *et al.*(238), although interpretation of this is limited both by the fact that the cases were identified though hospital episodes, and classification criteria were not applied, which potentially could lead to an underestimate of the rate of blindness in those with GCA. In addition using care episodes, rather than individual patient records, could lead to the potential for double or multiple counting.

A lower mean inflammatory marker result was noted in those with blindness, which reached statistical significance for CRP but not for ESR, in keeping with other studies. It is possible that patients with lower inflammatory markers at baseline assessment are at greater risk of blindness due to prior inadequate treatment with glucocorticoids; equally this factor may contribute to diagnostic delay, or reflect a propensity for inflammation in smaller vessels. Prior peripheral vascular disease was also identified as a risk factor for blindness in patients with GCA. Previous studies have implicated hypertension, a past history of ischaemic heart disease, thrombocytosis, constitutional symptoms, and low inflammatory response as potential risks for blindness (188, 198, 199). Reports have

been inconsistent and while many of these factors were not confirmed in the present study, taken together these findings suggest a potential role of endothelial dysfunction in both the development of GCA and its ischaemic complications. The increased risk of CVD following a diagnosis of GCA is also consistent with this hypothesis (239).

11.2.0 SOURCES OF BIAS

In observational data, the main sources of bias relate to sampling bias, information bias and confounding, the latter of which is dealt with a subsequent section in this chapter. Selection bias relates to the way participants were recruited and how representative they are of the population from which they derive. However in the context of this thesis information bias relates to the measurement error contributed through misclassification of either cases or covariates.

11.2.1 Selection bias

All the datasets used in this thesis are at risk of selection bias. The GCANS study had a single eligibility criteria for participants with an age over 55 years. However, those who had previously stated a wish not to be involved in research, those who were resident in a nursing home or considered too unwell to take part were excluded from the postal questionnaire, although all GP recorded diagnoses of PMR and GCA registered in the GP database were reviewed. In addition the resultant

cumulative prevalence estimates were minimum estimates preventing an upward bias of the estimate.

EPIC-Norfolk is a large cohort study within the wider EPIC initiative which was set-up in 1989 (240), and in terms of anthropometry, serum lipids and blood pressure the cohort is similar to the national population samples studied in the Health Survey of England (211). Although the third health checks ran over seven years when the participants were aged between 48 and 92 years, staff followed a tight protocol minimising variation, differences in interpretation and reducing subjectivity (241). However, it is possible that patients with worse vision would face challenges in attending the third health check follow-up and therefore the results of visual assessment could be biased towards those with better vision.

With DCVAS recruiting from 129 sites from 26 countries worldwide, the sampling bias arises from referral bias due to the fact that it was clinic-based, rather than population-based. However, the sample was not selected from one individual specialty or specialist centre, providing potentially greater generalisability than earlier single-centre studies.

11.2.2 Information bias

Observational epidemiological analyses are particularly prone to information bias through misclassification. However, the contribution to measurement error is likely due to be non-differential misclassification as

covariates were not recorded differently between cases and controls. This is most likely for the EPIC-Norfolk cohort as eventual disease status was not known at the time of baseline assessment.

With respect to misclassification, in all three datasets cases have been assessed using similar definitions of disease status and importantly, those cases fulfilling current classification criteria which is a major strength of this work.

11.3.0 INTERPRETATION OF THE FINDINGS

The data available within EPIC-Norfolk contributed greatly to the descriptive epidemiology and assessment of aetiological hypotheses in this thesis. Interpretation of these findings warrants further discussion. Inferences drawn rely on the analytical methods used and model assumptions and their implications are discussed in the following section.

11.3.1 Model assumptions

The use of logistic regression was appropriate for the data when using case-control study design. Confounding by age is likely given the difference in the crude and adjusted odds ratios. The subsequent models used appropriate analytical methods taking account of the confounders.

The association of PMR and GCA with age and traditional cardiovascular risk factors highlighted the potential contribution of mortality in modifying results of any analytical modelling. The use of Cox-proportional

hazards with Fine-Gray extension was appropriate for the analyses since the assumption of proportionality was not violated. The data for PMR and GCA occurrence may suggest that a continuous hazard assumption also applies, particularly through the effect of age and female sex (see section 6.1.0) and therefore appropriate to also be analysed using Poisson regression.

11.3.2 Confounding

There is no statistical test for confounding. Although in modelling, attempts were made to negate the effects of confounding, there could still be unknown or residual confounders.

However, as these results are broadly in keeping with other published estimates, they appear unlikely due to chance.

11.3.3 Limitations

The limitations of each of the analyses are discussed below. Particular challenges were faced in applying classification criteria retrospectively, particularly for the GCANS study. In addition, GCANS was a relatively small study despite the effort required in setting up and carrying out postal survey to 4,728 people, there were only 23 cases of GCA on the GP electronic record.

Over the course of 20 years of follow-up, the baseline variables assessed as part of the EPIC-Norfolk study are likely to have changed with many

more participants developing hypertension, for example. Therefore resultant estimates for the contribution for LDL and PMR should be viewed as a potential underestimate, compared to the true effect. The analysis of medication and subsequent diagnosis of PMR and or GCA is limited due to the single time point at which data was collected and the grouping of medication together. In addition doses and individual agents were unknown preventing a more comprehensive analysis.

For DCVAS, blindness was recorded as part of the VDI assessment but formal systematic ophthalmic evaluation was not undertaken for all participants. It is difficult to comment fully on the detailed causal pathways involved in patients whose symptoms evolved over the six months of follow-up, although only two patients without any visual disturbance at baseline were declared blind in one eye at six months. Our analysis of obesity and blindness needs to be treated with caution due to the relatively high proportion of missing values for BMI in this dataset. There is no information regarding the initial dose, route or timing of glucocorticoid therapy or anti-platelets such as aspirin. However, recent registry-based studies of GCA (239, 242) have not included glucocorticoid treatment as a separate covariate, as its use is advised as standard management for GCA (93), and therefore it was not considered possible to separate the effect of treatment and disease. To date this is the largest study of visual loss in cases of clinically-confirmed GCA and provides a robust estimate of blindness associated with a diagnosis of GCA. Blindness, both monocular and binocular, remains a major problem

in GCA and this study emphasises the need to be especially vigilant of this outcome in patients with a higher conventional vascular risk.

11.4.0 GENERALISABILITY AND APPLICATION OF THE FINDINGS

These findings need to be interpreted in light of the fact that most of the participants were Caucasian and of European descent, although this is not unique amongst studies of PMR and GCA with higher estimates of disease incidence and prevalence from Northern European latitudes and North America.

Major strengths of the analyses are that classification criteria have been applied to cases of PMR and GCA for all the datasets, which allows comparison to other studies which have similarly applied classification criteria.

The results of the analyses, should be representative to the UK population more generally.

11.4.1 The Public health implications

These are the first estimates for the UK for PMR and GCA incidence and prevalence and to apply classification criteria in over 30 years. They reveal the strong association with age which, due to the changing demographic of the UK, will likely have increasing importance with regard to healthcare delivery. The association of traditional cardiovascular risk

factors for both disease onset and progression is a worry and adds further importance to tackling these.

The results from DCVAS show that sight loss remains a major concern with GCA with around one in twelve patients blind in one eye by six months after diagnosis. Most patients who developed blindness did so by the time of their first assessment, with only two patients without symptoms of visual disturbance suffering blindness at six months. These results re-emphasise the need for urgent referral and rapid use of glucocorticoid therapy (236). The DCVAS analysis shows an association between blindness and peripheral vascular disease and these individuals may warrant closer follow-up.

For the other main consequence of disease progression of this thesis, namely IP in PMR, the current EULAR/ACR recommendations for PMR conditionally recommend methotrexate to patients at high risk of relapse (44). The expert panel list these risks as: female sex, ESR >40 mm/hr and peripheral inflammatory arthritis at baseline diagnosis but then add that a number of studies failed to demonstrate an association between these factors and relapse (44). The results from the EPIC-Norfolk data suggest that males, ever-smokers, those with synovitis and positive serology are at increased risk of IP and it is these patients who would most likely benefit from early introduction of DMARDs.

The shared clinical features between PMR and IP are a diagnostic challenge for clinicians. Serological testing for rheumatoid factor (RhF)

appears to be of limited clinical utility, with a relatively high proportion of PMR (21.8%) and IP (27.3%) cases having positive serology. Selecting a higher cut-off of >50 U/ml improves the specificity for RhF (18.2% IP cases being positive and only 4.5% of PMR cases being positive) resulting in a hazard ratio of 3.93 (95% CI 1.33, 11.65). Although improvement in specificity has been reported previously (243), relying on the presence of RhF or ACPA serology as the sole diagnostic feature would result in many undiagnosed cases of both IP and RA. Conversely, requiring an absence of rheumatoid factor or anti-ccp antibodies for a diagnosis of PMR would be unhelpful in view of the recognised increased prevalence of auto-antibodies in older people, particularly in women. Indeed a longitudinal study of 79 patients thought to have PMR showed that by 12 months, 72 were thought to have likely or definite PMR and anti-ccp antibodies were positive in up to 20 (28%) depending on the isotype of the antibody; IgM (n=20), IgA (n=3), IgG (n=1) (244). Ultimately clinicians must remain vigilant for diagnostic transformation when managing patients with PMR.

11.5.0 FUTURE DIRECTIONS

The major novelty of this thesis is the use of digital retinal imaging to record vascular morphology. The results show widened venules in participants with PMR which is in keeping with an effect of cardiovascular disease. Validation of such findings is needed in other large studies and work is currently underway to perform similar analyses within UK Biobank. In addition, as the data from the third health-check are from a

single time-point investigation of the longitudinal relationship of retinal vascular change is a potential avenue of further scientific discovery.

11.5.1 Improving the clinical measurement of disease in PMR and GCA

Further extensions of the variation in phenotype of cases of PMR and GCA are possible but require collaborative effort from large consortia. The assessment of disease activity of PMR and GCA also requires urgent attention. These latter problems are being addressed by the Outcome Measures in Rheumatology (OMERACT) group in which the author is involved. Key domains of Core, Mandatory, Research and contextual have been identified for the development of a new outcome measure set in for use in study of patients with PMR. Identification and evaluation of instruments which map onto these domains is the next step of the process.

11.5.2 Pharmocoepidmiology approaches

The analyses of the contribution of medications to the diagnosis of PMR and GCA is limited in this thesis due to the single time-point at which participants were recruited. The intended aims to investigate how medications might modify the disease course and morbidity profile of participants with GCA, were not possible due to small numbers. In addition the precise time-point at which participants started their medication contributed to left censoring. The data available from EPIC-

Norfolk precluded any more detailed or complicated analysis. Despite these problems, use of anti-hypertensives was associated with a reduced risk for PMR and when a combined hypertension variable was used, was associated with a reduced risk for both PMR and GCA. These findings would seem to go against the hypothesis that traditional cardiovascular risk factors are risk factors for PMR and GCA and it is possible that they are due to chance. However, in a recent analysis of traditional cardiovascular risk factors and length of stay amongst those patients admitted with acute coronary syndromes revealed hypertension and hyperlipidaemia were associated with a reduced length of stay (245). The authors speculate that this was because patients with these risk factors may be treated more aggressively leading to better outcome, but due to incomplete data are unable to certain of this conclusion (245). Similarly, although current BSR guidelines recommend the use of low-dose aspirin to prevent ischaemic complication in the condition, a study from eight UK secondary care centres revealed those taking aspirin prior to diagnosis had increased odds for ischaemic manifestations with an OR of 2.81 (95% CI 1.06, 7.45) (190) although this could represent confounding by indication and identify those with increased risk for peripheral vascular disease and those with previous myocardial infarction.

However the author is currently undertaking further work using a large community-based register to explore the effect of medication and outcomes in PMR and GCA using the CPRD to investigate the effect of medications and ocular outcomes in patients with PMR and GCA.

11.6.0 CONCLUSIONS

This thesis has addressed the evidence gaps in the epidemiology of PMR and GCA using large datasets with detailed clinical phenotype necessary to apply classification criteria. Classification criteria are not intended for the purpose of diagnosis and therefore it is not intended that all diagnosed cases will met their intended classification set. However, by defining cases both pragmatically and subsequently by those which meet their intended classification set the estimates can be compared to other contemporary studies.

This is an important area to study because of the lack of clarity of disease definition, the fact it is manged in the community, and the lifelong disease course. At time this work was started it was one of the most poorly characterised rheumatic diseases epidemiologically, despite PMR being as least as common as rheumatoid arthritis. Management was rooted in the past, and the risk of complications not known.

This work has provided up to date data on occurrence, and for the first time looked at risk factors for occurrence prior to the onset of disease, and the risk factors for progression. Traditional cardiovascular risk factors have emerged as a risk factors and a potential route for prevention. The work has started to lay the foundations for ocular screening using automated processing, and identified promising avenues in retinal vasculometric measures that will be taken forward in future projects.

The results from this work confirm the strong positive association with age and as the proportion of the population over 50 years old rises the importance of these not uncommon conditions will intensify particularly given the type and nature of associated morbidity. Traditional cardiovascular risk factors appear to be important as both risk factors for disease onset and progression and may point towards more careful monitoring for complications amongst those with peripheral vascular disease and GCA.

The analysis from the contribution of medications to modify the outcome of patients with PMR and GCA is limited due to lack of information on prescriptions and dosage variation over time. This problem is currently being addressed by the author using more definitive data sources, including the Clinical Practice Research Data Link (CPRD) which is a governmental, not-for-profit research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA), a part of the Department of Health.

The use of automated processing for analysing data on retinal morphology is a novel and important development in assessing aetiological hypotheses of disease, particularly those with an underlying vascular dysregulation mechanisms. Although the results for this work require replication in other datasets before firm conclusions can be drawn and this will form part of the intended post-doctoral work by the author

including large international datasets of retinal images and may be applicable to other rheumatic diseases.

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APPENDICES

Appendix 1 – Questionnaire for GCANS

Giant Cell Arteritis in Norfolk and Suffolk

(GCANS)

Dr Max Yates, Dr Richard Watts, Prof Alex MacGregor and Karly Graham are independent researchers working at the University of East Anglia in the United Kingdom and are carrying out a research project. This is called 'Giant Cell Arteritis In Norfolk and Suffolk (GCANS)'. The purpose of the study is to explore the occurrence of Giant Cell Arteritis in Norfolk and Suffolk.

Please take time to help by filling in this questionnaire. You do not need to give your name and your answers are strictly confidential. It may take approximately 5 -10 minutes of your time to complete.

- **What is your date of birth? Day Month Year**
- **Are you..? Male Female**

	Questions. *Please*	**Yes**	**No**

	*circle **Y** or **N**:*		
1	**Have you had pain in your jaw or tongue when chewing food (not toothache)?** • **If yes to 1, did you also have a headache at the same time?** • **If yes to 1, was this… (*please circle)*** **Within the last 6 mths 6 mths to 5 yrs More than 5 yrs ago**	Y Y	N Y
2	**Have you ever had double vision and/or a sudden loss or reduction in eye sight, even if temporary?** • **If yes to 2, did you also have a headache at the same time?** • **If yes to 2, was this… (*please circle)*** **Within the last 6 mths 6 mths to 5 yrs More than 5**	Y Y	N N

	<u>yrs ago</u>		
3	**Do you suffer of have you suffered with severe headaches lasting longer than 7 days at a time?** • **If yes to 3, was this… (*please circle)*** **<u>Within the last 6 mths</u>** **<u>6 mths to 5 yrs</u>** **<u>More than 5 yrs ago</u>**	Y	N
4	**Has your scalp over your temples been sore (eg was it painful to brush your hair)?** • **If yes to 4, did you also have a headache at the same time?** • **If yes to 4, was this… (*please circle)*** **<u>Within the last 6 mths</u>** **<u>6 mths to 5 yrs</u>** **<u>More than 5 yrs ago</u>**	Y Y	N N

5	**Have you woken up with stiffness or aching in your shoulders which lasted longer than 1 hour?** • **If yes to 5, did you also have a headache at the same time?** • **If yes to 5, was this… (*please circle)*** **<u>Within the last 6 mths</u> <u>6 mths to 5 yrs</u> <u>More than 5 yrs ago</u>**	Y Y	N N
6	**Have you ever had unexplained weight loss (not through dieting or exercise)?** • **If yes to 6, did you also have a headache at the same time?** • **If yes to 6, was this… (*please circle)*** **<u>Within the last 6 mths</u> <u>6 mths to 5 yrs</u> <u>More than 5 yrs ago</u>**	Y Y	N N
7	**Have you ever had a feeling of being general unwell with**	Y	N

	achy muscles lasting longer than 2 weeks? • **If yes to 7, did you also have a headache at the same time?** • **If yes to 7, was this… (*please circle)*** **<u>Within the last 6 mths</u>** **<u>6 mths to 5 yrs</u>** **<u>More than 5 yrs ago</u>**	Y	N
8	**Have you ever been given a diagnosis of Giant Cell Arteritis or Temporal Arteritis?** • **If yes to 8, which year was this?** _____	Y	N
9	**Have you ever been given a diagnosis of Polymyalgia Rheumatica (PMR)?** • **If yes to 9, which year was this?** _____	Y	N
10			

	Do you get migraines?	Y	N
	• **If yes to 10, do you get visual disturbance?**	Y	N
	• **If yes to 10, do you feel sick or vomit?**	Y	Y

Thank you for taking the time to complete this questionnaire.

Please return it with 2 copies of the consent form in the postage paid envelope provided.

Appendix 2 - Proposed Retinal Grading

A retinal grading system was carried out based on the National Health and Nutrition Examination Survey (NHANES) programme used for national ocular screening.

Photo Quality

QUARTZ is fully automated in its assessment of retinal images. However around 6% of images are wrongly graded as being unreadable by the software.

Focus

If retinal vessels are sharply defined or slightly fuzzy and small lesions such as retinal microaneurysms and small drusen are visible, the grade is "Good/Fair", code=0. If clarity is decreased so that small retinal lesions might be missed but larger lesions such as geographic atrophy, can be seen, the grade is "Borderline", code=1. If there is a pronounced decrease in sharpness where detail of larger lesions cannot be recognized, the grade is "Poor", code=2.

Illumination

If an image is poorly illuminated or overexposed, or there are pockets of uneven illumination (a dark macula) then Illumination should be graded “Yes”, code=2.

Field Definition

EPIC-Norfolk images are foveal focused – a traditional Field 2 image in the diabetic retinopathy screening programme. If the field deviates more than one disc diameter from the optimum location then Field Definition should be graded "Yes", code=2.

Haze

When a green/white halo or partial halo; or a green/white cast throughout the entire photograph is noted, Haze should be graded "Yes", code=2.

Dust

White dots or spots that may be varying size but are in the same location of the image no matter what field of the retina is imaged are usually caused by one or more dirty lenses on the camera. When dust or dirt spots are prominent or located in just the wrong place and cause difficulty in grading, Dust should be graded "Yes", code=2.

Lashes

Lashes or a partial blink often appear on the bottom of the image as either light or dark linear "shadows". These "shadows" can easily obscure the lower half of the image. Occasionally lashes will appear in the upper half of the image as a bright reflectance but do not affect the ability to

grade as much. When lashes (or a blink) are present Lashes should be coded “Yes”, code =2.

Arc

A small pupil or incorrect patient-to-camera distance can cause a crescent shaped arc to appear on the image, which can range in colour from yellow orange to blue, and in size from a small slice to an arc that obscures more than half of the field. Normally arcs are found along the nasal or temporal margin rather than the superior or inferior margins although they can occur anywhere. When an arc is present the grade should be “Yes”, code = 2.

Asteroid Hyalosis

Multiple spherical and stellate opacities in the vitreous may be difficult to differentiate in non-stereoscopic photographs and should appear in front of vessels and disc. Care must be taken to differentiate from retinal drusen. If asteroid hyalosis is dense, this may prevent grading drusen.

Gradeability

The grader will judge the overall quality of both images to determine the gradeability. If the field are focused clearly enough to image the retina, optic nerve and blood vessels without any portion missing or obscured, the image is considered completely gradable. If more than 75% of optic nerve cannot be graded, but it is possible to grade the blood vessels, the

grade is "Disc ungradable", code=1. If a portion of blood vessels, between 25% and 75 % cannot be graded, but the optic nerve is gradable, the grade is "Portion blood vessels ungradable", code=2.

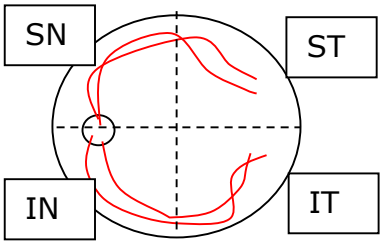
If more than 75% of the blood vessels are in poor focus, missing, or obscured by a retinal haemorrhage, vitreous haemorrhage, asteroid hyalosis or some other condition and no lesion of any type is seen but it is possible to grade the disc, the grade is " blood vessels ungradable", code=3.

If a portion of the disc and the blood vessels are ungradable (between 25-75% or each), the grade is code=4. If neither the disc nor the blood vessels can be graded (more than 75% of each), but other portions of the retina are visible, the grade is code=5. If no part of the fields can be graded, the grade is code=6.

Vascular Lesions

Each quadrant, superior temporal (ST), superior nasal (SN), inferior temporal (IT) and inferior nasal (IN) is evaluated for the absence or presence of vascular lesions or changes (see Figure S.2).

Figure S.2 Quadrants of a retinal fundus image



The following codes are used:

- Focal narrowing

Code Definition

0 No focal narrowing.

1 Questionable focal narrowing.

2 Definite focal narrowing

8 Cannot grade.

- Arterio-venous crossing abnormalities BVO/CVO (branch vein occlusion/central vein occlusion)

Each quadrant, superior temporal (ST), superior nasal (SN), inferior temporal (IT) and inferior nasal (IN) is evaluated for the absence of presence of AV nicking. The following codes are used:

Code Definition

0 No AV nipping.

1 Questionable AV nipping.

2 Definite AV nipping.

8 Cannot grade.

- BAO/CAO (branch artery occlusion/central artery occlusion)

Branch Vein Occlusion: Obstruction of a branch retinal venule. An older occlusion may demonstrate sheathed venules and retinal collateral vessels. Localised haemorrhages and/or IRMAs are commonly present. The occluded vessel may not always be obvious.

Central Vein Occlusion: Obstruction of a central retinal venule. A fresh occlusion is distinguished by dilated retinal venules and diffuse retinal haemorrhages.

Branch/Central Artery Occlusion: Obstruction of a branch or central retinal arteriole. If "fresh", may be associated with large greyish-white area of retinal infarction. Either generalised or localised ischaemia may be noted.

- Hollenhorst Plaque

Cholesterol emboli: These highly-refractile to smudgy-white lesions lie within arterioles and may be seen at artery bifurcations. Care must be

taken to distinguish from old retinal macroaneurysms or underlying drusen.

Retinal pigment atrophy

This lesion appears as a sharply defined area of drop-out of retinal pigment epithelium and choriocapillaries, exposing choroidal vessels as a result of degeneration of the deep layers of the retina. When atrophic lesions are definitely not a result of ARM, any other "Other" should be marked and a comment included. Similar to the other vascular lesions, each quadrant (ST, SN, IT, IN) was graded on the presence of retinal epithelial loss.

Tigroid or Tessellated Fundus

Graded as three indices of fundus tessellation: non, weakly and strongly tessellated.

Disc

Assessment of discs is coded as follows:

"0" – normal

"1" – atrophy

"2" – large disc

"3" – pale

"4" – cupping

"5" – laminar dot sign present

"6" – thick neuroretinal rim (NRR) / small cup

"7" – blurred nasal edge

"8" – blurred temporal edge

Peripheral Atrophy

PPA coded as none "0", presenting on temporal sided "1", present on nasal side "2", circumferential "3", and inferior "4".

Description

There is a description variable. This is field is completed when there is a relevant comment required, for example: the presence of drusen, cotton wool spots, tortuous vessels, thick venules, thin arterioles, or myopic atrophy.

Appendix 3 – Published Papers

Two original articles and two editorials published as a result from the work in this thesis appear in the following pages.