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ORIGINAL RESEARCH

# Metabolic features and glucocorticoid-induced comorbidities in patients with giant cell arteritis and polymyalgia rheumatica in a Dutch and Danish cohort

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## ABSTRACT

**Objectives** Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are age-associated inflammatory diseases that frequently overlap. Both diseases require long-term treatment with glucocorticoids (GCs), often associated with comorbidities. Previous population-based cohort studies reported that an unhealthier metabolic profile might prevent the development of GCA. Here, we report metabolic features before start of treatment and during treatment in patients with GCA and PMR.

**Methods** In the Dutch GCA/PMR/SENEX (GPS) cohort, we analysed metabolic features and prevalence of comorbidities (type 2 diabetes, hypercholesterolaemia, hypertension, obesity and cataract) in treatment-naïve patients with GCA (n=50) and PMR (n=42), and compared those with the population-based Lifelines cohort (n=91). To compare our findings in the GPS cohort, we included data from patients with GCA (n=52) and PMR (n=25) from the Aarhus cohort. Laboratory measurements, comorbidities and GC use were recorded for up to 5 years in the GPS cohort.

**Results** Glycated haemoglobin levels tended to be higher in treatment-naïve patients with GCA, whereas high-density lipoprotein, low-density lipoprotein and cholesterol levels were lower compared with the Lifelines population. Data from the Aarhus cohort were aligned with the findings obtained in the GPS cohort. Presence of comorbidities at baseline did not predict long-term GC requirement. The incidence of diabetes, obesity and cataract among patients with GCA increased upon initiation of GC treatment.

**Conclusion** Data from the GCA and PMR cohorts imply a metabolic dysregulation in treatment-naïve patients with GCA, but not in patients with PMR. Treatment with GCs led to the rise of comorbidities and an unhealthier metabolic profile, stressing the need for prednisone-sparing targeted treatment in these vulnerable patients.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Some evidence points at an association of a healthy metabolic profile with the development of giant cell arteritis (GCA).

### WHAT THIS STUDY ADDS

⇒ At diagnosis, patients with GCA in two GCA/polymyalgia rheumatica cohorts show a dysregulated lipid and glucose metabolism.

⇒ After glucocorticoid treatment initiation, the incidence of diabetes, obesity and cataract increased.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ At diagnosis, metabolic features may reflect the inflammation state in patients with GCA.

⇒ Novel glucocorticoid-sparing agents are needed for reducing adverse events in patients with GCA.

## INTRODUCTION

Giant cell arteritis (GCA) is a granulomatous inflammatory disease that affects large-sized and medium-sized vessels in elderly patients. Symptoms can vary, and the spectrum of disease includes overlapping phenotypes which are large vessel GCA and GCA with cranial artery involvement.[1] In addition to specific symptoms such as headache, jaw claudication, limb claudication and vision loss, patients also often suffer from non-specific symptoms such as fever and weight loss.[2 3] Moreover, due to the involvement of the aorta and its major branches, there is a risk of developing thoracic aneurysms, which significantly increases mortality among these patients.[3 4] Approximately 40%–60% of patients with GCA also have overlapping polymyalgia rheumatica (PMR).[2] PMR is an inflammatory rheumatic disease characterised by pain and stiffness of the hips and shoulder girdle. Similar to GCA, patients may also experience general symptoms.[5 6] PMR

is one of the most common rheumatic diseases in the elderly.[7]

Previous population-based cohort studies have reported that the risk of GCA development associates with a healthy metabolic profile.[8–11] High fasting blood glucose, cholesterol and triglyceride levels were found to be negatively associated with the development of GCA. Moreover, a negative correlation between body mass index (BMI) and the risk of developing GCA was shown.[8–11] However, these studies included individuals who developed GCA after inclusion in population-based cohorts, and studies on treatment-naïve patients with GCA are mostly lacking. Additionally, high glycated haemoglobin (HbA1c) levels might be negatively associated with a GCA diagnosis.[12] However, for patients with PMR, such an association with BMI was not detected.[13]

Both GCA and PMR require a prompt treatment with glucocorticoids (GCs). The recommended starting dose for PMR is 12.5–25 mg/day of prednisone, while in GCA treatment, a substantially higher dose of 40–60 mg/day is used.[14] GC tapering is initiated after clinical remission and is continued until GC-free remission is achieved, which in many patients, requires more than 2 years.[14 15] Also, relapses are common during GC tapering, requiring an increase in GC dose and prolonging treatment duration.[16]

Besides the relation between metabolic characteristics of patients at baseline and the risk of developing GCA and PMR, treatment with high-dose GCs increases the risk of GC-related adverse events. These adverse events include an increased BMI, hypercholesterolaemia (HCT), hypertension (HT), type 2 diabetes (T2D), cataract, glaucoma, pneumonia and infections.[17–25] Recent reports have stressed the importance of identifying new factors/biomarkers that could aid the stratification of patients with GCA/PMR for responsiveness to GC treatment and identification of alternative new GC-sparing treatment options.[26]

Thus, although recent studies suggest a positive association between a healthy metabolic profile in elderly individuals and the risk of development of GCA, data are limited. Therefore, we performed an in-depth characterisation of the metabolic features and prevalence of comorbidities of patients with GCA and PMR at the time of diagnosis, and compared those with age-matched and sex-matched individuals from the population-based cohort (Lifelines) from the same region. To contextualise our findings, patients with GCA and PMR from the Aarhus GCA and PMR cohort were studied. Next, we explored the association of metabolic features or comorbidities with inflammation markers at diagnosis. Furthermore, we investigated whether patient characteristics, comorbidities and intoxication at baseline predicted long-term GC requirement. Finally, we documented comorbidities after initiation of GC treatment during 5-year follow-up.

## MATERIALS AND METHODS

### Study populations

Two prospective GCA and PMR cohorts were included in this study. In both cohorts, none of the patients used GCs or disease-modifying antirheumatic drugs (DMARDs) before assessment. All study participants gave written informed consent and all procedures were in line with the Declaration of Helsinki.

Patients with newly diagnosed GCA (n=50) and PMR (n=44) were recruited from the GCA/PMR/SENEX (GPS) cohort in Groningen, the Netherlands. All patients were seen at the Rheumatology and Clinical Immunology outpatient clinic of the University Medical Center Groningen, in the period between 2011 and 2019. Diagnosis of patients with GCA was based on either a positive temporal artery biopsy (TAB) or 18F-fluorodeoxyglucose-positron emission tomography-CT (FDG-PET/CT). PMR diagnosis was based on either the Chuang/Hunder or American College of Rheumatology 2012 classification criteria together with the clinician's expert opinion and supported by FDG-PET/CT imaging. Patients who had been diagnosed with overlapping GCA and PMR were grouped with the patients with GCA.[27]

The Danish Aarhus cohort served as the validation cohort and included 52 patients with GCA and 25 patients with PMR who were diagnosed after clinical examination, laboratory analysis, the positivity of TAB, FDG-PET/CT and ultrasound imaging. Previously, a more detailed description of this cohort has been published.[28]

Cross-sectional data of the Lifelines cohort study (https://www.lifelines.nl/) were used as representative of the general population in the Netherlands. Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167 729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. Non-fasting participants from this cohort were selected for population-based comparison with our GPS cohort using frequency matching according to age and sex (n=93).[29]

### Follow-up and treatment

Participants with GCA and PMR in the GPS cohort received follow-up according to a fixed study protocol. In this study, for patients with GCA and PMR, clinical and laboratory data from follow-up visits at 3 months, 1, 2, 3, 4 and 5 years were included (online supplemental table 1 for time frames). GC treatment and tapering were in line with the British Society for Rheumatology (BSR) guidelines for GCA and PMR.[14] Six patients with PMR received treatment different from the BSR guidelines due to personal preferences and therefore only their baseline data were included. A relapse required an extra visit to the outpatient clinic and the daily GC dose was increased

and/or either methotrexate, leflunomide was added as GC-sparing treatment. In patients in remission, GC and/or DMARD tapering was continued until GC-free remission was achieved.

### Laboratory measurements

Laboratory measurements of HbA1c, glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, cholesterol, C reactive protein (CRP), erythrocyte sedimentation rate from GCA/PMR cohorts were collected as part of patient care and have previously been described extensively.[23] Details with respect to collection and processing of samples from the Lifelines population have been published before.[29]

### Comorbid diseases

Frequencies of common comorbidities such as T2D, HCT, HT, obesity and cataract were recorded. To include potentially undiagnosed comorbidities, metabolic disorders were also defined based on laboratory measurements and/or data from physical examination. These retrospectively defined comorbidities can be found in online supplemental table 2. All definitions were based on reference values. To cohere with HbA1c standardisation established by the International Federation of Clinical Chemistry Working Group, any HbA1c value in percentages was converted to mmol/mol. Cataract was also included as a comorbidity in this study, since it develops frequently during GC treatment.

### Patient and public involvement

In 2010, the GPS (GCA, PMR) cohort study including clinical data and biobanking was initiated. Questionnaires and patient-reported outcomes were designed in close contact with patients and the Dutch Vasculitis Foundation. Our central research question concerns stratification of patients. During our GPS cohort study, we have continuously partnered with our patients and asked for feedback on the burden of study. The latest renewal of our ethical approval in 2017 of the GPS cohort was based also on the input patients gave us.

### Statistical analysis

Results were expressed as number (%) of patients for categorical data and mean±SD or median (range) for normally distributed and non-normally distributed continuous data, respectively. $X^2$ test followed by $X^2$ or Fisher's exact test were used to compare differences in categorical parameters between the Dutch GCA, PMR and Lifelines groups. Kruskal-Wallis test followed by Mann-Whitney U test were used to compare differences in continuous parameters between these three groups. $X^2$ or Fisher's exact test and Mann-Whitney U test were used as appropriate to compare differences between the Dutch and Danish GCA or PMR groups as well as between subgroups with and without comorbidities. Spearman correlation coefficient was used to analyse the association between metabolic features and inflammation markers. Logistic generalised estimating equation (GEE) was performed to analyse comorbidities over time within subjects. GEE is a longitudinal analysis technique which makes use of all available longitudinal data and allows unequal numbers of repeated measurements. Missing data were not imputed. GEE corrects for the within-subject correlation using an a priori defined 'working' correlation structure. The exchangeable correlation structure was used for all variables. Simple contrasts were used to compare baseline and follow-up visits. Cox regression was performed to analyse patient characteristics, comorbidities and intoxication at baseline to predict time to achieve GC-free remission. P values of <0.05 were considered statistically significant. Statistical analysis was performed and graphs were made with IBM SPSS Statistics V.23 and GraphPad Prism for Windows V.8.0.1.

## RESULTS

### Patient characteristics

Baseline characteristics of patients with GCA and PMR of the Dutch GPS cohort were compared with data obtained from age-matched and sex-matched participants of the Dutch Lifelines cohort as representatives of the general population (table 1).

### Comorbidities and intoxication at diagnosis

We did not observe a lower prevalence of T2D in patients with GCA at diagnosis when compared with the general population (table 1). The percentage of T2D was even higher in patients with PMR. The prevalence of HT and cataract was significantly higher both in patients with GCA and PMR compared with the general population controls. Interestingly, the proportion of current smokers in the GCA group was significantly higher compared with patients with PMR, whereas the number of alcohol consumers was significantly lower. The frequency of comorbidities was comparable between patients from the GPS cohort and patients from the Aarhus cohort, except for HT, which was less common in patients with GCA in the Aarhus cohort which may be influenced by age difference between two cohorts.

### Altered glucose and lipid metabolism in patients with GCA at diagnosis

From our cross-sectional analysis at baseline, it appeared that markers of glucose and lipid metabolism had shifted in opposite directions in patients with GCA. At diagnosis, we observed significantly higher glucose levels in patients with GCA of the GPS cohort compared with the general population. Moreover, HbA1c levels tended to be higher in patients with GCA as well, when compared with individuals from the general population (p=0.068). In contrast, these patients with GCA had significantly lower cholesterol, HDL and LDL levels, and a lower BMI compared with controls. There were fewer differences between patients with PMR and the general population. We observed higher glucose levels and lower LDL levels in patients with PMR, whereas BMI, HbA1c levels and

**Table 1** Overview of patients with GCA/PMR from the Dutch GPS cohort and the Dutch general population cohort

| | GCA (GPS) | PMR (GPS) | Lifelines population | Kruskal-Wallis p value |
|---|---|---|---|---|
| N (total) | 50 | 44 | 93 | |
| Age in years, median (range) | 71.0 (52–89) | 73.0 (54–84) | 70.0 (52–85) | 0.096 |
| Female, n (%) | 35 (70) | 26 (59) | 61 (66) | 0.538 |
| Diagnosis (TAB/PET-CT/both), n | 23/33/9 | —/31/— | — | |
| Patients with GCA diagnosed with overlapping PMR | 12 | NA | — | |
| Fulfilled Chuang criteria, % (yes/no) | 67 (8/4) | 74 (32/11) | — | |
| Fulfilled ACR criteria, % (yes/no) | 72 (36/14) | 20 (9/35) | — | |
| Fulfilled ACR/EULAR criteria, % (yes/no) | 42 (5/7) | 86 (38/6) | — | |
| Duration of symptoms (days), median (range) | 47 (7–365) | 97 (30–479) | — | |
| Follow-up duration in months, median | 49 (0–63.9) | 49 (0–62.1) | — | |
| Weight loss,% (yes/no) | 62 (31/19) | 50 (20/19) | — | |
| Physical measurements | | | | |
| BMI, median (range, N) | 24.3 (19.5–33.9, 33) | 26.6 (17.8–40, 35) | 26.0 (18–42, 93) | 0.122 |
| Systolic blood pressure (mm Hg), median (range, N) | 140.0 (84–185, 42) | 140.0 (120-185, 39) | 134.0 (93–185, 93) | 0.070 |
| Diastolic blood pressure (mm Hg), median (range, N) | 79.5 (54–95, 42) | 80.0 (70–105, 39)*† | 72.0 (55–108, 93) | <0.0001 |
| Laboratory measurements | | | | |
| CRP (mg/L), median (range, N) | 54.0 (5–215, 49) | 42.0 (3.2–186, 39) | NA | |
| ESR (mm/hour), median (range, N) | 94.0* (9–121, 49) | 57.0 (7–109, 39) | NA | |
| HbA1c (mmol/mol), median (range, N) | 43.0 (35–69, 31) | 40.0 (35–74, 29) | 40.0 (33–64, 90) | 0.187 |
| Glucose (mmol/L), median (range, N) | 6.0 (5–10, 18)† | 5.7 (4.9–9.6, 15)† | 5.3 (2.8–14.7, 93) | 0.002 |
| Triglycerides (mmol/L), median (range, N) | 1.1 (0.6–2.4, 16) | 1.0 (0.7–2.1, 10) | 1.1 (0.5–3.6, 93) | 0.999 |
| Cholesterol (mmol/L), mean (±SD, N) | 4.0 (1.8–5.7, 23)†* | 4.9 (3.8–6.7, 13) | 5.4 (3.6–8.4, 93) | <0.0001 |
| HDL (mmol/L), mean (±SD, N) | 1.1 (0.1–1.9, 20)† | 1.5 (0.7–2.1, 12) | 1.7 (0.9–2.6), 93 | <0.001 |
| LDL (mmol/L), median (range, N) | 2.2 (0.8–4, 20)† | 2.7 (1.8–4.5, 12)† | 3.5 (2–6.5, 93) | <0.0001 |
| Comorbidities and intoxication | | | | |
| Type 2 diabetes, % (yes/no/NA) | 12 (6/44/0) | 23 (10/34/0) | 11 (10/83/0) | 0.151 |
| Hypercholesterolaemia, % (yes/no/NA) | 22 (11/39/0) | 14 (6/38/0) | 18 (17/47/29) | 0.274 |
| Hypertension, % (yes/no/NA) | 66 (33/17/0)† | 55 (24/20/0)† | 24 (22/44/27) | 0.002 |
| Cataract, % (yes/no/NA) | 14 (7/43/0)† | 16 (7/37/0)† | 11 (10/0/83) | <0.0001 |
| Obesity, % (yes/no/NA) | 12 (4/29/17) | 26 (9/26/11) | 22 (20/73/0) | 0.356 |
| Current smoker, % (yes/no/NA) | 31 (15/33/2)* | 11 (4/34/6) | 18 (17/74/2) | 0.051 |
| Ex-smoker, % (yes/no/NA) | 29 (14/34/2)† | 37 (14/24/6)† | 47 (44/1534) | <0.0001 |
| Alcohol usage, % (yes/no/NA) | 40 (18/27/5)* | 64 (23/13/8) | NA | 0.044 |

Group differences were reported with Kruskal-Wallis p value. The missing values were reported as NA.
*Significant difference between patients with GCA and PMR within the GPS cohort.
†Differ significantly from the general population.
ACR, American College of Rheumatology; BMI, body mass index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; GCA, giant cell arteritis; GPS, GCA/PMR/SENEX; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, total sample number that is included for analysis; NA, not available; PET, positron emission tomography; PMR, polymyalgia rheumatica; TAB, temporal artery biopsy.

other lipid markers were not altered (table 1). Of note, glucose levels were only recorded in a subset of patients.

To validate the findings described above by comparing those with measurements in the Aarhus cohort, baseline characteristics of patients with GCA and PMR from the GPS cohort were compared with the Aarhus cohort as comparison cohort in table 2. GPS cohort patients were slightly older at diagnosis than patients with GCA and PMR

**Table 2** Patient demographics and laboratory and clinical parameters of patients with GCA/PMR from the GPS and Aarhus cohorts

| | GCA (GPS) | GCA (Aarhus) | P value for GCA (GPS) versus GCA (Aarhus) | PMR (GPS) | PMR (Aarhus) | P value for PMR (GPS) versus PMR (Aarhus) |
|---|---|---|---|---|---|---|
| N (total) | 50 | 52 | | 44 | 25 | |
| Age in years, median (range) | 71.0 (52–89) | 67.0 (51–84) | 0.118 | 73.0 (54–84) | 68.0 (55–85) | 0.071 |
| Female, n (%) | 35 (70) | 32 (61) | 0.409 | 26 (59) | 13 (52) | 0.619 |
| Diagnosis (TAB/PET-CT/both), n | 23/33/9 | 2/14/34 | | —/31/— | NA | |
| Patients with GCA diagnosed with overlapping PMR | 12 | 20 | | NA | NA | |
| Fulfilled Chuang criteria, % (yes/no) | 67 (8/4) | 17 (9/43) | | 74 (32/11) | 68 (17/8) | |
| Fulfilled ACR criteria, % (yes/no) | 72 (36/14) | 84 (44/8) | | 20 (9/35) | 8 (2/23) | |
| Fulfilled ACR/EULAR criteria, % (yes/no) | 42 (5/7) | 7 (4/48) | | 86 (38/6) | 68 (17/8) | |
| Duration of symptoms, median (range) | 47 (7–365) | 88 (14–560) | | 97 (30–479) | 56 (28–306) | |
| Follow-up duration in months, median | 49 (0–63.9) | NA | — | 49 (0–62.1) | NA | — |
| Weight loss,% (yes/no) | 62 (31/19) | 86 (44/7)* | 0.006 | 50 (20/19) | 44 (11/14)† | |
| Physical measurements | | | | | | |
| BMI, median (range, N) | 24.3 (19.5–33.9, 33) | 23.2† (17.3–30.8, 50) | 0.118 | 26.6 (17.8–40, 35) | 26.4 (19.7–34.9, 25) | 0.642 |
| Systolic blood pressure (mm Hg), median (range, N) | 140.0 (84–185, 42) | 135.0 (97–184, 47) | 0.610 | 140.0 (120-185, 39) | 137.5 (104–190, 21) | 0.972 |
| Diastolic blood pressure (mm Hg), median (range, N) | 79.5 (54–95, 42) | 76.5† (51–100, 47) | 0.431 | 80.0 (70–105, 39)‡ | 88.5 (68–106, 21) | 0.043 |
| Laboratory measurements | | | | | | |
| CRP (mg/L), median (range, N) | 54.0 (5–215, 49) | 74.0† (10–182, 52) | 0.106 | 42.0 (3.2–186, 39) | 35.0 (5–199, 25) | 0.740 |
| ESR (mm/hour), median (range, N) | 94.0‡ (9–121, 49) | 72.5† (20–120, 52) | 0.543 | 57.0 (7–109, 39) | 53.0 (8–83, 25) | 0.463 |
| HbA1c (mmol/mol), median (range, N) | 43.0 (35–69, 31) | 41.0 (33–77, 52) | 0.327 | 40.0 (35–74, 29) | 39.0 (33–49, 25) | 0.188 |
| Glucose (mmol/L), median (range, N) | 6.0 (5–10, 18) | NA | – | 5.7 (4.9–9.6, 15) | NA | – |
| Triglycerides (mmol/L), median (range, N) | 1.1 (0.6–2.4, 16) | 0.9† (0.5–1.8, 52) | 0.085 | 1.0 (0.7–2.1, 10) | 1.2 (0.9–2.5, 25) | 0.158 |
| Cholesterol (mmol/L), mean (±SD, N) | 4.0 (1.8–5.7, 23)‡ | 4.1† (2.5–5.8, 52) | 0.998 | 4.9 (3.8–6.7, 13) | 4.5 (3.1–6.1, 25) | 0.126 |
| HDL (mmol/L), mean (±SD, N) | 1.1 (0.1–1.9, 20) | 1.2 (0.5–2.5, 52) | 0.903 | 1.5 (0.7–2.1, 12)* | 1.3 (0.6–1.9, 25) | 0.046 |
| LDL (mmol/L), median (range, N) | 2.2 (0.8–4, 20) | 2.3† (1–4.1, 52) | 0.771 | 2.7 (1.8–4.5, 12) | 2.7 (1.4–3.9, 25) | 0.465 |
| Comorbidities and intoxication | | | | | | |
| Type 2 diabetes, % (yes/no/NA) | 12 (6/44/0) | 15 (8/44/0) | 0.775 | 11 (10/83/0) | 8 (2/23/0) | 0.188 |

Continued

**Table 2** Continued

| | GCA (GPS) | GCA (Aarhus) | P value for GCA (GPS) versus GCA (Aarhus) | PMR (GPS) | PMR (Aarhus) | P value for PMR (GPS) versus PMR (Aarhus) |
|---|---|---|---|---|---|---|
| Hypercholesterolaemia, % (yes/no/NA) | 22 (11/39/0) | 15 (8/44/0) | 0.452 | 18 (17/47/29) | 24 (6/19/0) | >0.999 |
| Hypertension, % (yes/no/NA) | 66 (33/17/0) | 38* (18/34/0) | 0.003 | 24 (22/44/27) | 36 (9/16/0) | 0.210 |
| Cataract, % (yes/no/NA) | 14 (7/43/0) | NA | — | 11 (10/0/83) | NA | — |
| Obesity, % (yes/no/NA) | 12 (4/29/17) | 6 (3/47/0) | 0.428 | 22 (20/73/0) | 9 (2/23/0) | 0.101 |
| Current smoker, % (yes/no/NA) | 31 (15/33/2)‡ | 27 (14/38/0) | | 18 (17/74/2) | 12 (3/22/0) | |
| Ex-smoker, % (yes/no/NA) | 29 (14/34/2) | 38 (20/32/0) | | 47 (44/15/34) | 28 (7/18/0) | |
| Alcohol usage, % (yes/no/NA) | 40 (18/27/5)‡ | NA | | 64 (23/13/8) | NA | |

*Significant difference between GPS and Aarhus cohort.
†Significant difference between patients with GCA and PMR within Aarhus cohort.
‡Significant difference between patients with GCA and PMR within the GPS cohort.
ACR, American College of Rheumatology; BMI, body mass index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; GCA, giant cell arteritis; GPS, GCA/PMR/SENEX; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not available; PET, positron emission tomography; PMR, polymyalgia rheumatica; TAB, temporal artery biopsy.

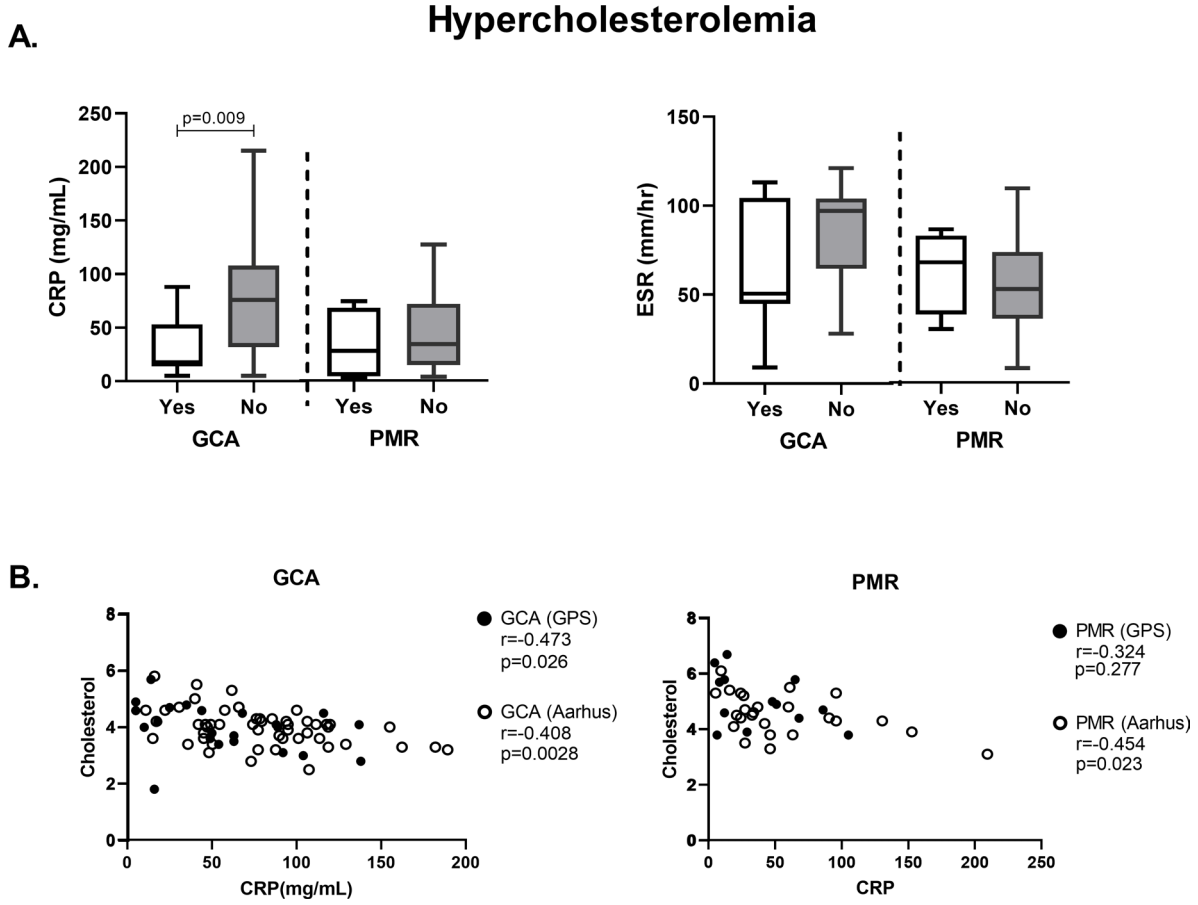


**Figure 1** The association of baseline concurrent hypercholesterolaemia in the GPS cohort (A) and cholesterol levels in both cohorts (B) with inflammation markers: CRP and ESR. Eleven out of 50 patients with GCA (GPS) and 6 out of 44 patients with PMR (GPS) were diagnosed with hypercholesterolaemia. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; GPS, GCA/PMR/SENEX; PMR, polymyalgia rheumatica.

in the Aarhus cohort. Except HT, there were no significant differences regarding the proportion of comorbidities of patients with GCA between GPS and Aarhus cohort. The data on laboratory measurements, metabolic features and comorbidities were in line with the findings in the GPS cohort (table 2). Levels of markers of HbA1c and lipid metabolism were comparable in patients with GCA/PMR of both cohorts.

### Comorbidities and metabolic features in relation to inflammation markers

We next compared whether levels of acute-phase markers were associated with comorbidities in patients with GCA and PMR of the GPS cohort. CRP levels of patients with GCA with HCT were lower than in patients with GCA without HCT (figure 1A). As active inflammation may have an impact on BMI, glucose and lipid metabolism, we correlated metabolic features with inflammation markers. Indeed, the CRP levels were negatively associated with total cholesterol levels in patients with GCA in both cohorts (figure 1B). We also observed negative correlations between lipid markers and inflammatory markers in patients with PMR of both cohorts (online supplemental figure 1A). Other associations of metabolic comorbidities with acute-phase markers can be found in online supplemental figure 1A. Additionally, we found that patients with GCA who reported weight loss at baseline had significantly higher CRP levels (online supplemental figure 1B). This may be linked to a longer-lasting inflammation, as a lower BMI was significantly correlated with the symptom duration. Surprisingly, patients with GCA and PMR reporting weight loss did not have a lower BMI compared with patients who did not report weight loss (online supplemental figure 1B).

### Prediction of GC treatment based on patient characteristics and comorbidities at diagnosis

Next, we analysed the effect of age, gender, comorbidities and intoxication (smoking and alcohol usage) at baseline on the time to achieve GC-free remission, as longer duration of GC treatment indicates an unfavourable disease course. In patients with PMR, age significantly prolonged the GC duration. The presence of obesity, T2D, HCT, HT and cataract, as well as smoking and alcohol usage, at the time of GCA and PMR diagnosis, was not significantly associated with either a longer or shorter time to GC-free remission (figure 2A,B).

### GC treatment effect on developing comorbidities in patients with GCA and PMR

Finally, we recorded changes in metabolic comorbidities during 5-year follow-up. The recorded proportion of

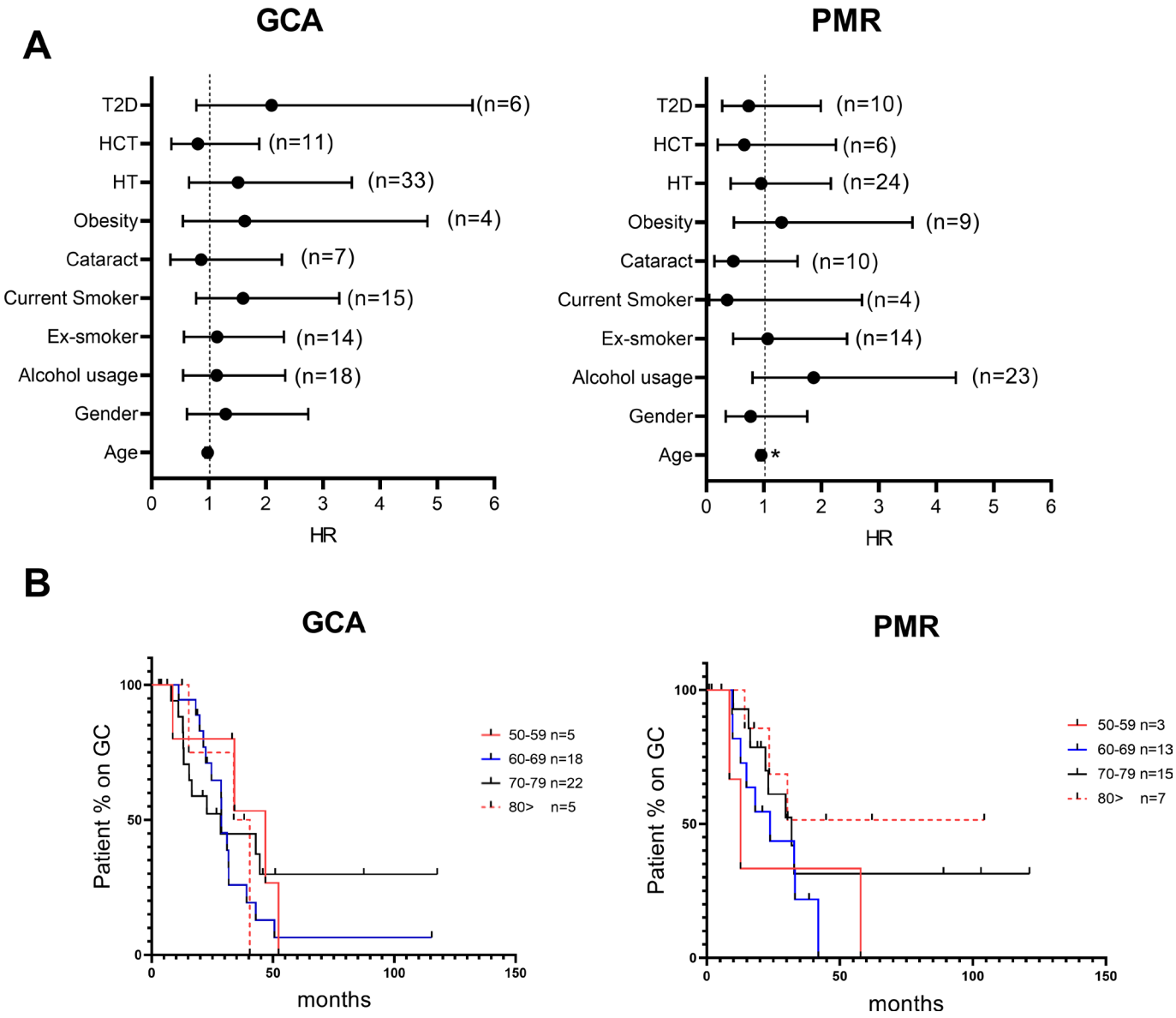


**Figure 2** The impact of age, comorbidities, smoking and alcohol usage at time of diagnosis on reaching GC-free remission in patients with GCA and PMR. (A) HRs and (B) Kaplan-Meier curve stratified for age subgroups. Dashed line is the cut-off for the HR. HR >1 (with 95% CI >1): higher chance to reach GC-free remission, HR <1 (with 95% CI <1): a lower chance to reach GC-free remission. *P<0.05. GC, glucocorticoid; GCA, giant cell arteritis; HCT, hypercholesterolaemia; HT, hypertension; PMR, polymyalgia rheumatica; T2D, type 2 diabetes.

patients with T2D was significantly increased in patients with GCA at 3 months (p<0.001) and 1 year (p=0.022) compared with baseline (figure 3). The proportion of patients with obesity was significantly increased in patients with GCA at 2, 4 and 5 years of follow-up. An increase of cataract in patients with GCA at 3 and 4 years was observed as well. In patients with PMR, the incidence of comorbidities did not significantly change over time when compared with baseline.

## DISCUSSION

In this study, we aimed to assess the differences between metabolic features and comorbidities in treatment-naive patients with GCA/PMR and general population, and analyse the GC effect on patients with GCA/PMR. To this end, we analysed the prevalence of comorbidities and levels of metabolic markers in two cohorts of patients with GCA/PMR at diagnosis, and compared these with data from age-matched participants in the Lifelines population cohort. We show that generally, markers associated with glucose metabolism appear to be higher in patients with GCA than in the general population, whereas the opposite was found for markers associated with lipid metabolism. We also assessed the impact of patient characteristics, comorbidities and intoxication on the time to achieve GC-free remission, and found them unsuited to aid in stratification for favourable and non-favourable disease outcomes.

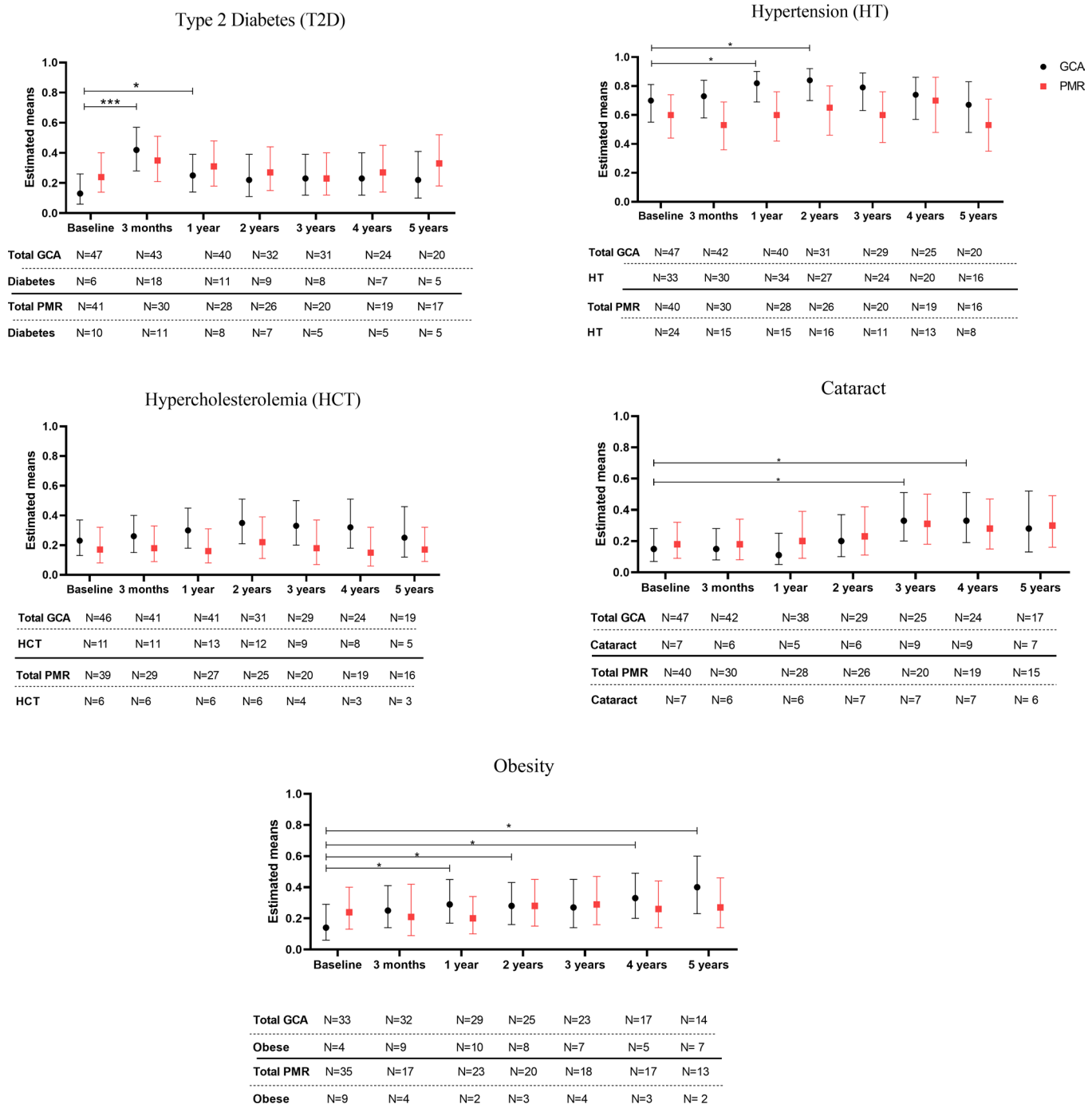


**Figure 3** Comorbidities in patients with GCA and PMR after initiation of GC treatment during 5-year follow-up. Error bars show estimated means with 95% Wald CI (GEE modelling). Black dots represent patients with GCA, while red squares represent patients with PMR. *P<0.05, **p<0.01, ***p<0.001. GC, glucocorticoid; GCA, giant cell arteritis; GEE, generalised estimating equation; PMR, polymyalgia rheumatica.

Finally, we documented the effect of GC treatment on the development of comorbidities.

Our cross-sectional analysis at the time of diagnosis showed a disturbed glucose metabolism in patients with GCA. Previous studies had suggested that HbA1c levels and the prevalence of diabetes are lower at the time of GCA diagnosis.[12 30] However, in our cohort, we showed that glucose levels are elevated in patients with GCA at baseline when compared with the general population, whereas HbA1c levels are unchanged.[12] The discrepancy between our findings and other studies may be due to differences in study design, for example, the recording of metabolic features, size of the studies or due to differences in inclusion criteria of patient groups. In the study by Mukhtyar *et al*[12] (n=112 cases, n=224 controls), the median (IQR) HbA1c level of the patients with GCA and controls was 40 (37–43) and 41 (39–47) mmol/mol, respectively. In the GPS cohort, this was 43 (40–44) for

patients with GCA and 40 (37–43) in the general population. It therefore appears that although the medians of the studies are comparable, the distribution range of HbA1c levels differs. In particular, the control population of the study by Mukhtyar *et al* included a number of participants with very high HbA1c levels. These controls were individuals suspected of having GCA, and both patients with GCA and controls had likely been using GCs, which also influence HbA1c levels. Therefore, the control group in this study may not reflect the general population, which probably explains the differences. Importantly, our study is the first study on metabolic features and comorbidities in treatment-naïve patients, in two GCA/PMR cohorts. In our study, the majority of patients had missing glucose values due to a change in standardised order sets in 2016; therefore, the results should be evaluated carefully.

The elevated glucose levels in patients with GCA may reflect current inflammation. A disturbed glucose metabolism has been described in other inflammatory diseases as well, such as rheumatoid arthritis (RA).[31 32] The more pronounced elevation of glucose levels compared with HbA1c levels may reflect faster response of blood glucose to inflammation, as HbA1c levels may show the long-term effect of disturbed glucose metabolism. Additionally, our group recently demonstrated that the cellular glucose metabolism, that is, glycolytic activity, reflects systemic inflammation in patients with GCA, which may assist the diagnosis and monitoring of disease activity.[33] This may support an important link between disturbed glucose metabolism and inflammation in patients with GCA. However, the lack of association between glucose markers and inflammatory markers in patients with GCA argues against this conclusion. One explanation could be that the ongoing inflammatory response in patients with GCA causes a disturbed glucose metabolism which is independent of the extent of the inflammatory response in individual patients.

In line with previous reports, we also observed lower total cholesterol, LDL and HDL levels in patients with GCA compared with the Lifelines population cohort.[16 18 19] A similar observation regarding low levels of cholesterol, LDL and HDL levels was also reported in patients with active psoriatic arthritis and RA.[34] In patients with PMR, we reported fewer alterations in lipid and glucose metabolism markers, and indeed, so far, such negative associations were not reported for PMR. One current hypothesis on altered lipid metabolism is that during the active disease stage, activated mononuclear phagocytes may scavenge the LDL particles and thereby lower the LDL concentration in serum. This hypothesis is in congruence with the lower CRP levels found in patients with GCA (GPS) with HCT and the negative correlation of total cholesterol levels with CRP and the negative correlation between lipid and inflammation markers in patients with PMR from both cohorts. Studies in RA support these findings, where treatment with tocilizumab (interleukin-6 receptor blockade) reversed LDL, cholesterol and triglyceride levels while reducing the inflammation.[34] In addition, the BMI of patients with GCA was lower compared with the general population, which is likely also due to inflammatory burden,[9] and indeed a substantial subset of patients did report recent weight loss. The weight loss increases with time, as evidenced by the association of BMI with symptom duration. In our cohort, patients with GCA who experienced weight loss had higher CRP levels compared with patients who did not report weight loss. Overall, these findings indicate that a detailed analysis of glucose and lipid metabolism may assist to define a pre-disease pattern for patients with GCA but that data on inflammation should be considered when analysing these data.

Possibly, differences in lifestyle (eg, smoking, alcohol) could increase the risk in individuals predisposed to age-associated autoinflammatory diseases.[35 36] As reported previously,[37] smoking may increase the risk of developing GCA. Indeed, in our cohort, we observed a higher percentage of current smokers in patients with GCA than in patients with PMR. This is in line with previous studies showing smoking as a risk factor for GCA development which is may be a result of a direct effect of smoking on endothelial cells.[37 38]

In an effort to identify markers that predict the patient disease course, we aimed to aid stratification of patients. Scott *et al* previously reported that obesity is associated with poorer outcomes in patients with PMR. [39] Here, we did not observe any effect of metabolic comorbidities such as T2D or obesity at baseline on the patients' disease course.[29] We did, however, observe that an older age (>80 years old) predicted longer GC treatment duration in patients with PMR, which is in line with a previously reported relation between age and risk of relapse in patients with PMR.[40]

Even though this cohort study may lack the power to detect smaller differences, we observed changes in comorbidities and metabolic health after initiation of GC therapy. Follow-up analysis revealed increased numbers of recorded T2D cases in patients with GCA at 3 months and 1 year after GC treatment compared with baseline. The recorded T2D cases subsequently normalised after 1 year of treatment and did not increase further at later time points during the follow-up. As this phenomenon was observed in patients with GCA but not patients with PMR, it may be that elevation of T2D cases was due to the high GC dosage in patients with GCA during the first months of treatment. Possible longer-term effects of GC treatment also appeared in patients with GCA only. The proportion of patients with cataract at 3 and 4 years increased, while obesity increased at 2, 4 and 5 years in patients with GCA. Thus, we observed less adverse events associated with GCs in patients with PMR, despite the fact that the treatment duration of both populations did not differ, indicating that particularly the high-dose GCs could be detrimental for the patients. Overall, these findings highlight the unwanted GC effects in patients and the need for novel GC-sparing therapeutic agents. Also, informing patients about the risk of an increase in weight

and development of cataract carries an importance. It should be kept in mind that longitudinal modelling of binary endpoints with missing values has its limitations. We compared follow-up visits with baseline to demonstrate that there is an increase in certain comorbidities after starting GC treatment in patients with GCA. The results observed in the GEE modelling were in line with the raw data, for example, an increase in T2D at 3 months. However, the exact estimation of the effect size and course over time is difficult and should be interpreted with caution.

Strengths of this study are the participation of two well-established treatment-naïve GCA and PMR patient cohorts as well as comparison of the Dutch GPS cohort with population-based controls from the same geographical region. Moreover, patients in the GPS cohort were prospectively followed for up to 5 years, allowing us to perform a prognostic analysis. A limitation is the fact that the number of patients during follow-up is relatively low, which impacts the power of our analysis on the development of new comorbidities. Prognostic analyses of disease outcomes based on baseline parameters may suffer from the same lack of power, possibly obscuring the existence of these prognostic parameters. Furthermore, the relatively small number of patients due to missing data did not allow us to correct for multiple testing in our comparative analyses, but the use of an external GCA/PMR cohort strengthened our findings.

In this prospective study, we investigated metabolic features and comorbidities associated with GCA and PMR development and the effect of GC treatment. Patients at baseline presented with disturbed glucose levels and lipid metabolism compared with the general population. Surprisingly, even though the lipid profile in patients was considered healthier than the profile of the general population, the glucose profile was considered unhealthier, the latter being in contrast with data obtained from population-based cohort studies. These alterations in metabolic features are likely linked to the inflammation in these untreated patients. During follow-up, patients developed GC-induced T2D, cataract and HT emphasising the urgent need for GC-sparing targeted treatment.

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**Contributors** IE and YvS conceived and designed the study. IE, BDN, PT, AvE and YvS acquired the data. IE, SA, BDN, PH, AB, EH, EB and YvS were involved in the data analysis and/or interpretation. IE and YvS drafted the manuscript, and all authors revised it critically for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. IE accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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**Patient consent for publication** Obtained.

**Ethics approval** This study involves human participants and ethical approval was obtained from the institutional review board of the UMCG, the Netherlands (METc2010/222) and the local ethical committee in Denmark (1-10-72-60-14). Participants gave informed consent to participate in the study before taking part.

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## REFERENCES

1 van der Geest KSM, Sandovici M, van Sleen Y, *et al*. Review: what is the current evidence for disease subsets in giant cell arteritis? *Arthritis Rheumatol* 2018;70:1366–76.
2 Dejaco C, Duftner C, Buttgereit F, *et al*. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. *Rheumatology* 2017;56:506–15.
3 González-Gay Miguel Á, Ortego-Jurado M, Ercole L. Giant cell arteritis: is the clinical spectrum of the disease changing? *BMC Geriatr* 2019;19:1–7.
4 Carvajal Alegria G, van Sleen Y, Graver JC, *et al*. Aortic involvement in giant cell arteritis. *Joint Bone Spine* 2021;88:105045.
5 Camellino D, Giusti A, Girasole G, *et al*. Pathogenesis, diagnosis and management of polymyalgia rheumatica. *Drugs Aging* 2019;36:1015–26.
6 Dejaco C, Duftner C, Dasgupta B, *et al*. Polymyalgia rheumatica and giant cell arteritis: management of two diseases of the elderly. *Aging health* 2011;7:633–45.
7 Dasgupta B, Salvarani C, Schirmer M, *et al*. Developing classification criteria for polymyalgia rheumatica: comparison of views from an expert panel and wider survey. *J Rheumatol* 2008;35:270–7.
8 Wadström K, Jacobsson L, Mohammad AJ, *et al*. Negative associations for fasting blood glucose, cholesterol and triglyceride levels with the development of giant cell arteritis. *Rheumatology* 2020;59:3229–36.
9 Jakobsson K, Jacobsson L, Warrington K, *et al*. Body mass index and the risk of giant cell arteritis: results from a prospective study. *Rheumatology* 2015;54:433–40.
10 Tomasson G, Bjornsson J, Zhang Y, *et al*. Cardiovascular risk factors and incident giant cell arteritis: a population-based cohort study. *Scand J Rheumatol* 2019;48:213–7.
11 Ungprasert P, Thongprayoon C, Warrington KJ. Lower body mass index is associated with a higher risk of giant cell arteritis: a systematic review and meta-analysis. *Ann Transl Med* 2015;3:1–7.

12 Mukhtyar C, Myers H, Jones C, *et al*. The relationship between glycated haemoglobin levels and the risk of giant cell arteritis - a case-control study. *Rheumatol Adv Pract* 2020;4:1–5.
13 Hoganson DD, Crowson CS, Warrington KJ, *et al*. Lack of association of high body mass index with risk for developing polymyalgia rheumatica. *Int J Rheum Dis* 2010;13:e1–5.
14 Dasgupta B, Borg FA, Hassan N, *et al*. BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology* 2010;49:1594–7.
15 Buttgereit F, Matteson EL, Dejaco C, *et al*. Prevention of glucocorticoid morbidity in giant cell arteritis. *Rheumatology* 2018;57:ii11–21.
16 Tuckwell K, Collinson N, Dimonaco S, *et al*. Newly diagnosed vs. relapsing giant cell arteritis: baseline data from the GiACTA trial. *Semin Arthritis Rheum* 2017;46:657–64.
17 Wilson JC, Sarsour K, Collinson N, *et al*. Incidence of outcomes potentially associated with corticosteroid therapy in patients with giant cell arteritis. *Semin Arthritis Rheum* 2017;46:650–6.
18 Wilson JC, Sarsour K, Collinson N, *et al*. Serious adverse effects associated with glucocorticoid therapy in patients with giant cell arteritis (GCA): a nested case-control analysis. *Semin Arthritis Rheum* 2017;46:819–27.
19 Best JH, Kong AM, Unizony S, *et al*. Risk of potential glucocorticoid-related adverse events in patients with giant cell arteritis: results from a USA-based electronic health records database. *Rheumatol Ther* 2019;6:599–610.
20 Lai LYH, Harris E, West RM, *et al*. Association between glucocorticoid therapy and incidence of diabetes mellitus in polymyalgia rheumatica and giant cell arteritis: a systematic review and meta-analysis. *RMD Open* 2018;4:1–9.
21 Proven A, Gabriel SE, Orces C, *et al*. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003;49:703–8.
22 Broder MS, Sarsour K, Chang E, *et al*. Corticosteroid-related adverse events in patients with giant cell arteritis: a claims-based analysis. *Semin Arthritis Rheum* 2016;46:246–52.
23 Savas M, Muka T, Wester VL, *et al*. Associations between systemic and local corticosteroid use with metabolic syndrome and body mass index. *J Clin Endocrinol Metab* 2017;102:3765–74.
24 Wu J, Mackie SL, Pujades-Rodriguez M. Glucocorticoid dose-dependent risk of type 2 diabetes in six immune-mediated inflammatory diseases: a population-based cohort analysis. *BMJ Open Diab Res Care* 2020;8:e001220–8.
25 Mazzantini M, Torre C, Miccoli M, *et al*. Adverse events during longterm low-dose glucocorticoid treatment of polymyalgia rheumatica: a retrospective study. *J Rheumatol* 2012;39:552–7.
26 Tomelleri A, van der Geest KSM, Sebastian A, *et al*. Disease stratification in giant cell arteritis to reduce relapses and prevent long-term vascular damage. *Lancet Rheumatol* 2021;3:e886–95.
27 Dasgupta B, Cimmino MA, Kremers HM, *et al*. 2012 provisional classification criteria for polymyalgia rheumatica: a European league against rheumatism/American college of rheumatology collaborative initiative. *Arthritis & Rheumatism* 2012;64:943–54.
28 Nielsen BD, Gormsen LC, Hansen IT, *et al*. Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. *Eur J Nucl Med Mol Imaging* 2018;45:1119–28.
29 Scholtens S, Smidt N, Swertz MA, *et al*. Cohort profile: lifelines, a three-generation cohort study and biobank. *Int J Epidemiol* 2015;44:1172–80.
30 Ungprasert P, Upala S, Sanguankeo A, *et al*. Patients with giant cell arteritis have a lower prevalence of diabetes mellitus: a systematic review and meta-analysis. *Mod Rheumatol* 2016;26:410–4.
31 Mishra KK, Pandey HP. A study on physiological changes in essential hypertension and rheumatoid arthritis with reference to the levels of cortisol, blood glucose, triglycerides and cholesterol. *Indian J Physiol Pharmacol* 1995;39:68–70.
32 Ristić GG, Subota V, Stanisavljević D, *et al*. Impact of disease activity on impaired glucose metabolism in patients with rheumatoid arthritis. *Arthritis Res Ther* 2021;23:95.
33 Esen I, Jiemy WF, van Sleen Y. Plasma pyruvate kinase M2 as a marker of vascular inflammation in giant cell arteritis. *Rheumatology* 2021.
34 Ferguson LD, Siebert S, McInnes IB, *et al*. Cardiometabolic comorbidities in RA and PsA: lessons learned and future directions. *Nat Rev Rheumatol* 2019;15:461–74.
35 Gwinnutt JM, Verstappen SM, Humphreys JH. The impact of lifestyle behaviours, physical activity and smoking on morbidity and mortality in patients with rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2020;34:101562.
36 Chang K, Yang SM, Kim SH, *et al*. Smoking and rheumatoid arthritis. *Int J Mol Sci* 2014;15:22279–95.
37 Brennan DN, Ungprasert P, Warrington KJ, *et al*. Smoking as a risk factor for giant cell arteritis: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2018;48:529–37.
38 Larsson K, Mellström D, Nordborg E, *et al*. Early menopause, low body mass index, and smoking are independent risk factors for developing giant cell arteritis. *Ann Rheum Dis* 2006;65:529–32.
39 Scott IC, Bajpai R, Hider SL, *et al*. O38 The relationship between obesity and outcomes in patients with polymyalgia rheumatica. *Rheumatology* 2020;59.
40 Van Hemelen M, Betrains A, Vanderschueren S, *et al*. Impact of age at diagnosis in polymyalgia rheumatica: a retrospective cohort study of 218 patients. *Autoimmun Rev* 2020;19:102692.