Supplementary Methods

UK GCA Consortium Cohort

A favourable ethical opinion for the UK GCA Consortium (UK GCA) study was granted by the Yorkshire and the Humber Leeds West Research Ethics Committee (05/Q1108/28). Patients were included if they had a consultant-confirmed (rheumatologist or ophthalmologist) diagnosis of giant cell arteritis (GCA). All participants provided written informed consent as previously described.(1) Participants were identified retrospectively from departmental and/or pathology records at 70 different NHS sites in Great Britain (England, Wales and Scotland) between 2005 and 2020. GCA was diagnosed between 1991-2020. Structured data collection was performed by patient interview and medical records review using a structured case report form (CRF).

Cases were also classified according to achievement of at least three out of five of the 1990 American College of Rheumatology (ACR) classification criteria:(2) (i) age at disease onset ≥ 50 years, (ii) new headache, (iii) temporal artery abnormality, (iv) ESR of 50 mm/hr or greater, and (v) abnormal TAB. In order to maximise our dataset, we imputed the ESR from CRP, since ESR was not routinely measured at several NHS sites in the UK during the study period. Missing variable percentile analysis was performed on all cases where both ESR and CRP values were available (n=1001). We demonstrated that for a value of 50mm/hr or more for ESR, the equivalent value for CRP was 36mg/L (9th percentile). Therefore, CRP values (in the absence of ESR) of ≥ 36 mg/L were used to impute ESR ≥ 50 mm/hr.

Results of the temporal artery biopsy (TAB) and diagnostic vascular imaging (computed tomography [CT], CT angiography [CTA], positron emission computed tomography with 2-deoxy-2-fluorine-18-fluoro-D-glucose [^{18}FDG-PET/CT], magnetic resonance angiography [MRA], or ultrasound scan [USS]) were documented, where available, and a subgroup of patients with a positive TAB and/or imaging confirmation of GCA were defined based on pathologists and radiologists reports. At the start of the recruitment window, not all cases of GCA had a confirmatory diagnostic test, as was standard practice in the UK at that time.

Retrospective application of 2022 ACR/ European Alliance of Associations for Rheumatology (EULAR) classification criteria was performed in response to reviewers comments, using data available from the

original UKGCA CRF(3). We accepted a pathologists report of a positive temporal artery biopsy and a sonographers report of a positive temporal artery ultrasound. We were unable to confirm whether Halos were present from all reports and did not have sufficient data to determine if bilateral axillary artery involvement was present. Likewise, many of the PET-CT scans did not have a structured report, where we could evaluate the SUVmax nor whether aortitis was present throughout the aorta or involved both axillary arteries with active aortitis was based on the radiologists report of active LVV/aortitis secondary to GCA. Application of the 2022 ACR/EULAR classification criteria, resulted in 283 cases being reclassified compared with the 1990 ACR classification criteria (51 cases switched from yes to no; 25 switch from no to yes and an additional 207 were recoded as yes from unknown).

Additional variables assessed in this study were:

Demographics at time of GCA diagnosis. Age; sex; ethnicity; family history of GCA; family history of polymyalgia rheumatica (PMR), body mass index (BMI); smoking status (never, ex or current at GCA diagnosis); alcohol intake (UK units(4))**;** area-level socio-economic deprivation (Index of Multiple Deprivation 2019; IMD2019). The IMD2019 is the UK government's preferred measure of socio-economic deprivation for England. It is a weighted, area-level aggregation of the following seven distinct domains of deprivation: income and employment (both 22.5%); education and health (both 13.5%); crime, barriers to housing and services, and living environment (all 9.3%). It has been calculated for each lower layer super output area (LSOA) in England (32,844 areas each containing an average of 1,500 individuals). They are ranked from 1 (most deprived) to 32,844 (least deprived).(5) Postcodes were converted to IMD2019 scores.(6) Post codes were available for 1,346/1,946 (64.7%) patients. These were ranked according to their Index of Multiple Deprivation rank (2019) and binned into five categories (quintiles): Q1 (lowest) n = 270, ≤ 10,797; Q2 n = 269, 10,797 – 18,331; Q3, n = 269, 18,331 – 23,753 ; Q4 n = 269, 23,753 – 28,614; Q5; (highest) n = 269, ≥ 28,614.

<u>Multi-dimensional GCA phenotypes documented at GCA diagnosis</u>

- **Cranial ischaemic manifestations (Supplementary Table 1)**. **A) Transient cranial ischaemic features. Ocular ischaemic features**: transient diplopia (DIP); transient double vision/absence of ocular motility (TDV); transient field defect (TFD); transient reduced acuity (TRA); transient vision loss (TVL). **Non-ocular cranial ischaemic features**: jaw claudication; tongue claudication; transient ischaemic attack (TIA) at presentation considered secondary to GCA. **B) Cranial ischaemic complications**. **Ocular complications**: Anterior ischaemic optic neuropathy (AION); branch retinal artery occlusion (BRAO); cilioretinal artery occlusion (CAO); cranial nerve palsy (CNP: III, IV or V); central retinal artery occlusion (CRAO); posterior ischaemic optic neuropathy (PION); relative afferent pupillary defect (RAPD); irreversible visual loss (PVL); irreversible visual field defect (PVFD); irreversible ocular motility; irreversible diplopia. **Non-ocular cranial complications:** Scalp necrosis; tongue necrosis; cerebrovascular accident (CVA) at presentation considered secondary to GCA.
- **Extra-cranial ischaemic features:** Arm claudication; leg claudication
- **Extra-cranial ischaemic complications:** fixed vascular stenosis to limb at presentation, secondary to GCA
- **Polymyalgia rheumatica (PMR) and polymyalgic symptoms**: Polymyalgic symptoms and/or a formal PMR diagnosis were recorded at the time of initial GCA diagnosis. Where PMR was diagnosed and treated with medium-dose glucocorticoids (e.g. 10-20mg prednisolone) prior to developing symptoms of GCA we classified these cases as having PMR prior to GCA, whereas untreated symptoms at GCA presentation were recorded as occurring at GCA presentation.
- **Systemic inflammatory response**. Weight loss; erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); platelet count measured at GCA presentation.
- **Established cardiovascular comorbidities.** Angina; myocardial infarction (MI); atrial fibrillation (AF); heart failure (HF); TIA (excluding those secondary to GCA at presentation); CVA (excluding those secondary to GCA at presentation); peripheral vascular disease (PVD); aortic aneurysm.
- **Established cardiovascular risk factors** diabetes; hypertension; hyperlipidemia.

- **Medication**. Prednisolone to treat GCA; antiplatelet; anticoagulant (including: apixaban, warfarin, dabigatran, edoxaban, enoxaparin, and rivaroxaban) and cholesterol-lowering drugs (including: atorvastatin, bezafibrate, ezetimibe, fenofibrate, pravastatin, rosuvastatin, simvastatin, and statin [type not indicated]), taken before onset of GCA.
- **Symptom duration**. Time from first symptom of GCA to first dose of prednisolone

Supplementary Table 1. Definitions of the primary and secondary outcomes in this study.

Outcome	Sub-division	Feature/Complication
Cranial ischaemic complications in GCA	Ocular complications	Anterior ischaemic optic neuropathy Branch retinal artery occlusion Cilioretinal artery occlusion Cranial nerve palsy (III, IV, or V) Central retinal artery occlusion Posterior ischaemic optic neuropathy Relative afferent pupillary defect Irreversible visual loss Irreversible visual field defect Irreversible ocular motility Irreversible diplopia
	Non-ocular complications	Scalp necrosis Tongue necrosis Cerebrovascular accident at presentation considered secondary to GCA
Transient cranial ischaemic features in GCA	Ocular ischaemic features	Transient diplopia Transient double vision/absence of ocular motility Transient field defect Transient reduced acuity Transient vision loss
	Non-ocular cranial ischaemic features	Jaw claudication Tongue claudication Transient ischaemic attack at presentation considered secondary to GCA
Extra-cranial ischaemic manifestations	Extra-cranial ischaemic features	Arm claudication Leg claudication
	Extra-cranial ischaemic complications	Fixed vascular stenosis to limb at presentation, secondary to GCA

UK Biobank Cohort

Data from the population-based, prospective UK Biobank cohort was also used in this work (National Research Ethics Committee approval: REC reference 11/NW/0382; project 24559). UK Biobank combines

biomarker, genetic, survey and electronic health record data of >500,000 participants aged 40 to 60 years at recruitment in 2006 to 2010.

Trait selection for polygenic risk score calculation

Traits selected for the optimization of polygenic risk scores (PRS) were guided by a literature review of cardiovascular (CV) related traits. This was performed using the PUBMED, MEDLINE and Web of Science literature search engines. Public databases were interrogated to identify publicly available genome-wide association study (GWAS) summary statistics for traits in white European populations. Where sample sizes for phenotypes were larger in UK Biobank data than publicly available GWAS, GWAS were performed in a white European subset of the full UK Biobank population (defined as those who self-reported 'White' ethnicity in baseline data and fell within the European cluster in PCA)(7) and PRS were calculated from the resulting summary statistics. Details of the traits for which PRS were calculated, as well as their respective GWAS publication (or UK Biobank field name) may be found in **Supplementary Table 2**.

Supplementary Table 2. List of traits for which polygenic risk scores were calculated

Trait	PMID/UKB field name (coding)-	Sample size of GWAS (cases/controls)	*N* SNPs in PRS
Cardiovascular diseases			
Angina[±]	UK Biobank - 20002 (1074)	12,581 / 384,679	94
Myocardial infarction	33532862	61,000 / 578,000	410
Atrial fibrillation	30061737	606,20 / 970,216	519
Heart failure	31919418	47,309 / 930,014	40
Transient ischaemic attack[±]	UK Biobank - 20002 (1082)	1,454 / 395,806	22
Stroke[±]	UK Biobank – 20002 (1081)	5,249 / 392,011	25
Peripheral vascular diease[±]	UK Biobank - 20002 (1067)	741 / 396,519	27
Abdominal aortic aneurysm	34737426	8,404 / 447,944	23
Thoracic aortic aneurysm	34265237	1,351 / 18,295	33
Thromboembolic disease[±]	UK Biobank - 20002 (1068 & 1094)	10,237 / 387,023	37
Cardiovascular risk factors			
Type 2 diabetes	30297969	74,124 / 824,006	771
Glycated haemoglobin[±*]	UK Biobank - 30750	373,823	1,456
Hyperlipidemia	34906840	39,961 / 309,261	669
Triglycerides	24097068	94,595	12
High density lipoprotein	24097068	94,595	403
Low density lipoprotein	24097068	94,595	365
Hypertension[±]	UK Biobank - 20002 (1065)	105,115 / 292,145	1,173
C-reactive protein	29875488	3,301	33
Platelet count[±]	UK Biobank - 30080	397,260	3,603
Body mass index[±]	UK Biobank - 23104	397,260	2,803
Basal metabolic rate[±]	UK Biobank - 23105	397,260	1,083
Body fat percentage[±]	UK Biobank - 23099	397,260	951
Waist-hip ratio[±]	UK Biobank - 48 / 49	397,260	749

[±]*A genome-wide association study was performed for this trait in UK Biobank data.*
***Individuals with type 1 or type 2 diabetes mellitus were removed from the cohort prior to GWAS of this trait.*
PMID, PubMed identification number; UKB, UK Biobank; GWAS, genome-wide association study; N, number; SNP, single nucleotide polymorphism; PRS, polygenic risk score.

UK GCA Cohort: genetic quality control

For the first two batches of UK GCA genetic data used in this work (*N batch 1 samples*=477, *N batch 2 samples*=239, of 1,936 total), genomic DNA from peripheral blood cells was extracted and sequenced using the "Infinium HumanCore Beadchip" and the Genotyping Module (v.1.9) of the GenomeStudio software (Illumina), as described in Carmona et al. (2017).(8)

An additional 1,220 GCA subjects ("batch 3") were newly genotyped prior to this study, with sequencing of genomic DNA from peripheral blood cells performed using the Illumina Infidium Global Screening Array.(9)

For all batches (*N*=1,936), sex chromosomes were removed from the analyses, and PLINK v.1.9.(10) was used to remove single nucleotide polymorphisms (SNPs) with call rates < 97%, variants deviating from Hardy-Weinberg equilibrium (HWE, *HWE* = 1.00 x 10^{-10}), and a MAF exclusion threshold calculated for each batch using a formula developed by Winkler et al. (2014)(11):

$$MAF = \frac{6}{2\,x\,N}$$

Where *N* is the number of samples in the batch (*batch 1 MAF* = 0.006, *batch 2 MAF* = 0.012, *batch 2 MAF* = 0.002). Samples with a missingness rate > 3% were removed, those who deviated > 3 standard deviations from the heterozygosity rate mean, and following linkage disequilibrium (LD) based pruning (high inversion rate regions removed, *window size* [*bp*] = 50, *window shift* [*SNPs*] = 5, *LD* R^2 = 0.20), all individuals with $\hat{p} > 0.20$ were removed (assuming that the GCA cohort is a random population sample). Finally, all non-A, T, C or G variants were removed, along with variants with missing alleles.

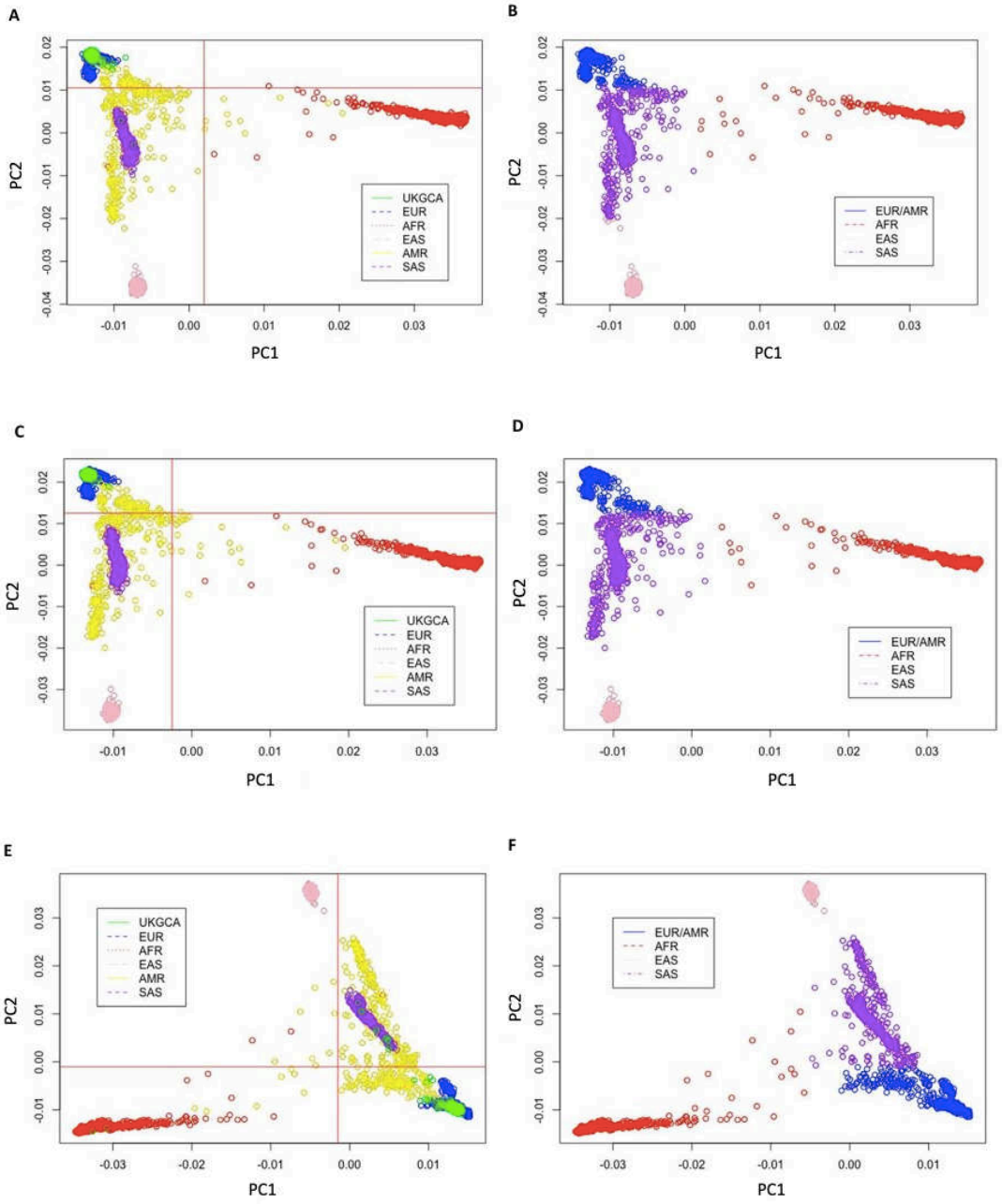
Due to the lack of overlapping genotyped variants between batches 1 and 2, and 3, PCA was performed independently (in PLINK v.1.09.)(10) for each cohort to cluster ethnicities and identify population outliers, for use in later analyses.

GCA data were parsed through the McCarthy group toolbox to conduct further QC, and imputation was performed on each batch independently using TopMed.(12) Imputation was performed separately for the

batches due to the lack of overlapping genotyped variants between batches 1 and 2 (combined), and batch 3. Finally, post-imputation QC was performed on the datasets, removing SNPs with an imputation $R^2 <$ 0.50, and data from the three batches were merged and lifted from GrCh38 to GrCh37 coordinates using the LiftOver tool.(13)

Definition of ethnicity using GCA genetic data

Since information on ethnicity was incomplete in the reported data, a novel ethnicity variable was formed using genetic data from the cohort. PCs from PCA performed on the three batches of the GCA cohort (analyses described earlier) were projected onto data from the 1000 Genomes consortium. GCA PCs were plotted with 1000 Genomes data and used to estimate ethnicities of individuals within the cohort (**Supplementary Figure 1**).(14)



Supplementary Figure 1: PCA plots of batch 1 (top), batch 2 (middle), batch3 (bottom), with UK GCA consortium patients mapped with 1000 Genomes reference samples. Left-hand plots display samples colour coded by reference ethnicity/UK GCA consortium membership, with "white European" cut-offs indicated by red lines. Right-hand plots represent newly defined sample ethnicities. UKGCA, United Kingdom giant cell arteritis consortium; EUR, European; AFR, African; EAS, east Asian; AMR, American; SAS, south Asian.

UK Biobank genetic quality control

Details of the genotyping and imputation of UK Biobank data have previously been described, both of which were performed centrally.(15) Briefly, one of two arrays (Affymetrix UK BiLEVE Axiom or Affymetrix UK Biobank Axiom array) were used to genotype participants. Combined reference panels from the Haplotype Reference Consortium,(16) 1000 Genomes and UK10K(17) projects were then used to further impute ~90 million genetic variants.

Further QC of the genetic data is described in Crossfield *et al*. (2022).(7) This included: the removal of samples with high heterozygosity or missingness rates, closely related individuals (2^{nd} degree relatives or closer) and where their self-reported sex did not match their genetic sex; an amendment to UK Biobank's definition of "white British ancestry" using multi-dimensional scaling; and further post-imputation QC to remove genetic markers with a MAF < 0.001 and imputation quality score < 0.80. A total of 10,152,250 genetic markers remained for analysis.

Genome-wide association studies and polygenic risk score calculation

For 12 traits, a GWAS was performed in white European UK Biobank data using linear or logistic regression in PLINK v1.9., including the top 10 PCs from PCA as covariates to adjust for population stratification.

PRS were calculated using the PRSice v2.3.3. tool with effect sizes from either publicly available GWAS summary statistics or GWAS performed in the UK Biobank data described above. SNPs from these GWAS were clumped (LD R^2 threshold=0.10, in 250kb blocks) and variants with a *P-value* association with the phenotype of $\leq 1.00 \times 10^{-5}$ (the "borderline association" threshold as described by the EBI GWAS catalog(18) were retained to form a PRS for the respective trait.

Univariable associations and optimization of an elastic net regression model

Univariable associations were first tested between CV-related traits/CVDs and cranial ischaemic complications in GCA, and those associations with an LR P-value ≤ 0.10 were included in elastic net regression, which was used as a variable selection tool in this work, removing redundant or highly

correlated variables. Whilst comparable tools may yield similar results, they are limited by drawbacks such as poor interpretability: as is the case with ridge regression, which shrinks coefficients but always retains all predictors in the final model;(19) and arbitrary variable dropping: as is the case with lasso regression, which removes subsets of correlated variables somewhat arbitrarily.(20) Elastic net regression balances the penalties used in these techniques to improve model regularization.(21)

To optimize the elastic net regression model, the respective dataset was first reduced to those samples with non-missing values for all variables and randomly split into a training and testing set using a 70:30 ratio. An elastic net model was trained by performing linear regression 20 times with an increasing alpha (α) from zero to one (in 0.05 increments). The α parameter was selected from the test with the lowest mean squared error and included as a parameter when optimizing the lambda (λ) parameter using k-fold cross-validation.

Once the elastic net regression model was optimized, it was used to aid variable selection and associations were tested in a multivariable regression model to yield effect estimates.

Susceptibility testing and pathway analyses

PRS with LR test *P-values* ≤ 0.05 in univariate regression for cranial ischaemic complications were tested for association with GCA susceptibility using a case-control approach (cases *N*=1,879, controls *N*=5,448). To further optimize these PRS, thereby gaining greater mechanistic insights, the clumping and thresholding approach was employed by the PRSice v2.3.3. tool,(22) testing PRS at several different *P-value* thresholds for association with GCA susceptibility and selecting an optimal PRS (the PRS with the greatest R^2 in linear/logistic regression). To adjust for the testing of multiple PRS for a single trait, a permutation test was applied, resulting in an empirical *P-value* for the association test.

The Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA) v1.4.0(23) tool was then used to perform pathway analysis on the SNPs in these optimized PRS. The FUMA package includes several tools to provide *in-silico* prediction of the functional and biological context for SNPs. These tools include the Multi-marker Analysis of GenoMic Annotation (MAGMA) gene-based and gene-set tests,(24) as well as the ANNOtate VARiation (ANNOVAR) tool.(25) FUMA also performs gene set

enrichment analysis (GSEA) with databases such as Reactome,(26) the Kyoto Encyclopedia of Genes and Genomes (KEGG) and the gene ontology (GO) database.(27, 28) In order to capture all *cis*-effects of SNPs in the PRS on local genes, positional gene mapping was performed using a maximum distance of 1megabase (Mb) of the gene transcript (a *cis* locus as defined by Yao et al. [2018](29)).

Supplementary Results

Patient Cohort

1,946 cases of GCA were recruited into this study, 1,324/1,424 cases (92.98%) fulfilled the imputed 1990 ACR classification criteria and 992/1,434 (69.18%) of these had a diagnosis supported by a confirmatory test (either TAB or imaging, as defined in **Supplementary Methods**).

Consistent with UK practice at the time the patients recruited to this study were diagnosed with GCA (1991-2021), not all patients had a confirmatory diagnostic test, particularly where there was believed to be a firm clinical diagnosis. 1,283 (65.93%) patients had a TAB performed (positive *N*=890; negative *N*=393), 495 (25.44%) did not have TAB performed, and it was not known whether the remaining 168 (8.63%) had a TAB procedure. A smaller number *N*=329 (16.91%) patients underwent a diagnostic imaging procedure. Of these 329 patients, 155 (47.11%) results were consistent with GCA. Of these with a positive diagnostic imaging result, 97 (29.48%) had a positive USS scan and 38 (11.55%) had a positive CT, CTA, 18FDG-PET/CT, MRA.

Comparison with UK Population data

Previous work has highlighted potential protective associations between some cardiovascular risk factors and GCA, including obesity, smoking status and diabetes mellitus.(30, 31) Therefore, population prevalences of these features were assessed in the GCA cohort and compared with UK national averages.

BMI

Participants had a lower BMI than the UK national average (BMI for males and females aged 65–74 years is 26.23 kg/m^2 and 26.45 kg/m^2 respectively, and 25.24 kg/m^2 and 25.71 kg/m^2 for males and female aged ≥ 75 years respectively).(32) 19.10% of patients (Female *N*=132, 9.92% all females; Male *N*=46, 7.58% of

all males) presented with a BMI ≥30 kg/m^2 (obese according to UK criteria) compared to population data of 32% obesity in adults aged 65–74 years, and 27% obesity in adults aged ≥ 75 years. The relationship between patient age at diagnosis (years) and BMI (kg/m^2) was investigated by estimating Pearson's correlation coefficient. There was a small, negative correlation between patient age and BMI (R^2=-0.17, DF=931, P=1.45 x 10^{-7}) with older patients having a lower BMI. These findings follow the UK trend that BMI decreases with age.

Smoking status

There was a higher proportion of participants that had "ever" smoked compared with the UK national average of those that reported to smoke (51.59% [*N*=809/1,568] of GCA patients reported to have "ever" smoked [Female *N*=506, 38.02% all females; Male *N*=299, 49.26% of all males]). However, a lower proportion of participants were current smokers at the time of diagnosis compared with the UK national average of reported smokers (13.31% [*N*=208/1,563] of GCA patients [Female *N*=141, 10.59% all females; Male *N*=66, 10.87% of all males]). The national average of those reported to smoke was 21% (21% of males and 20% of females) at the time of data collection.(33)

Compared with the UK national average for individuals aged 35 to 49 (23% total; 25% of males and 22% of females), the proportion of individuals who had "ever" smoked in this age group of GCA cohort was lower (0% [*N*=0/2] of this group, both female), as was the proportion of individuals who smoked at diagnosis (0% [*N*=0/2], both female).

In contrast, compared with the UK national average for individuals aged 50 to 59 (21% total; 23% of males and 20% of females), the proportion of individuals who had "ever" smoked in this age group of GCA cohort was higher in both males and females (49.51% [*N*=51/103] of this age range [Female *N*=31, 43.03% of females in this age range; Male *N*=20, 64.52% of males in this age range]), as was the proportion of individuals who smoked at diagnosis (49.51% [*N*=24/102] of this age range [Female *N*=17, 23.94% of females in this age range; Male *N*=7, 22.58% of males in this age range]).

Finally, compared with the UK national average for individuals aged 60 and over (12% total; 12% of males and 12% of females), the proportion of individuals who had "ever" smoked in this age group of GCA cohort

was higher in both males and females (51.72% [*N*=751/1,452] of this age range [Female *N*=474, 47.83% of females in this age range; Male *N*=277, 60.09% of males in this age range]), as was the proportion of individuals who smoked at diagnosis (12.5% [*N*=181/1,448] of this age range [Female *N*=123, 12.45% of females in this age range; Male *N*=58, 12.61% of males in this age range]).

Diabetes mellitus

Participants had a higher rate of diabetes mellitus diagnosis than the UK national average, with 14.01% (207/1,478) of GCA patients reported to have a prior diagnosis of diabetes mellitus at GCA diagnosis (Female *N*=120, 9.02% all females; Male *N*=86, 14.17% of all males), compared with a national average of 7% in males and 5% in females.(34) For 31.66% (*N*=468/1,478) of the GCA cohort, their diagnostic status of diabetes was unknown.

Index of multiple deprivation

When compared with UK population quintiles for the index of multiple deprivation, this cohort had a disproportionately high number of individuals in the "least deprived" areas (28.90% of cohort; 389/1,346), and a disproportionately low number of individuals in the "most deprived" areas (12.33% of cohort; 166/1,346).

Descriptive statistics of the full cohort

A total of 81.3% (N=1,583/1,946) of the GCA cohort had a diagnosis which fulfilled the imputed 2022 ACR criteria (**Supplmentary Table 3**). Additionally, 30.8% (N=442/1,434) had a diagnosis not confirmed by either temporal artery biopsy or vascular imaging. No considerable differences in demographics were observed between the total cohort and either of these groups.

Supplementary Table 3. Patient demographics at presentation: total GCA cohort; those fulfilling imputed 1990 ACR classification criteria; fulfilling imputed 2022 ACR/EULAR classification criteria; confirmed diagnosis by temporal artery biopsy or vascular imaging; diagnosis not confirmed by biopsy or imaging.

	Total cohort	Fulfilling imputed 1990 ACR classification criteria	Fulfilling imputed 2022 ACR/EULAR classification criteria*	Diagnosis confirmed by biopsy/imaging	Diagnosis not confirmed by biopsy/imaging*
	(*N*=1,946)	(*N*^{I}=1,324/1,424)	(*N*^{I}=1,583/1,669)	(*N*^{I}=992/1,434)	(*N*^{I}=442/1,434)
	MD (Q1 to Q3) or N (%)				
Age at diagnosis (years), median (IQR)	71 (66 to 77)	71 (66 to 77)	71.29 (66 - 77)	73 (68 to 78)	69 (64 to 75)
Female sex	1,331/1,938 (68.7%)	892/1320 (67.6%)	1087/1578 (68.9%)	663/992 (66.8%)	312/442 (70.6%)
Ethnicity					
EUR	1863/1878 (99.2%)	1273/1287 (98.9%)	1522/1534 (99.2%)	954/963 (99.1%)	419/423 (99.1%)
AFR	2/1878 (0.1%)	2/1287 (0.2%)	1/1534 (0.1%)	1/963 (0.1%)	1/423 (0.2%)
SAS	13/1878 (0.7%)	12/1287 (0.9%)	11/1534 (0.7%)	8/963 (0.8%)	3/423 (0.7%)
EAS	0/1878 (0%)	0/1287 (0%)	0/1534 (0%)	0/963 (0%)	0/423 (0%)
Family history of GCA	26/947 (2.8%)	21/758 (2.8%)	25/845 (3.0%)	11/448 (2.5%)	8/215 (3.7%)
Family history of PMR	42/939 (4.5%)	34/751 (4.5%)	39/838 (4.7%)	18/444 (4.1%)	12/214 (5.6%)
BMI (kg/m^2)					
<18.5	21/937 (2.2%)	15/756 (2.0%)	19/841 (2.3%)	13/454 (2.9%)	4/217 (1.8%)
18.5 to <25	383/937 (40.9%)	312/756 (41.3%)	355/841 (42.2%)	221/454 (48.7%)	61/217 (28.1%)
25 to <30	354/937 (37.8%)	284/756 (37.6%)	313/841 (37.2%)	160/454 (35.2%)	88/217 (40.6%)
≥ 30 kg/m^2	179/937 (19.1%)	145/756 (19.2%)	154/841 (18.3%)	60/454 (13.2%)	64/217 (29.5%)
Smoking tobacco (ever)	809/1,568 (51.6%)	660/1267 (52.1%)	735/1410 (52.1%)	413/795 (52.0%)	189/364 (51.9%)
Smoking tobacco at GCA diagnosis	208/1,563 (13.3%)	172/1263 (13.6%)	191/1406 (13.6%)	125/792 (15.8%)	49/363 (13.5%)

Alcohol units/week	5.05 (0 to 7)	5.38 (0 to 7)	5.24 (0 - 7)	5.41 (0 to 7)	4.42 (0 to 5)
Alcohol ≥ 14 units/week	110/1,147 (9.6%)	96/920 (10.4%)	105/1031 (10.2%)	58/565 (10.3%)	18/238 (7.6%)
Index of Multiple Deprivation 2019 (quintiles)					
1 (most deprived)	270/1,346 (20.1%)	187/885 (21.1%)	218/1074 (20.3%)	143/706 (20.3%)	66/280 (23.6%)
2	269/1,346 (20.0.%)	176/885 (19.9%)	214/1074 (19.9%)	146/706 (20.7%)	43/280 (15.4%)
3	269/1,346 (20.0%)	173/885 (19.6%)	206/1074 (19.2%)	130/706 (18.4%)	55/280 (19.6%)
4	269/1,346 (20.0%)	182/885 (20.6%)	220/1074 (20.5%)	143/706 (20.3%)	57/280 (20.4%)
5 (least deprived)	269/1,346 (20.0%)	167/885 (18.9%)	216/1074 (20.1%)	144/706 (20.4%)	59/280 (21.1%)

**Post-hoc analysis requested by reviewers.*

[1]Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.

ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology; MD, median; Q, quartile; N, sample number; EUR, white European (European/American); AFR, African; EAS, east Asian; SAS, south Asian; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; CV, cardiovascular disease; BMI, body mass index.

Of this cohort, 16.0% (N=327/1,925) had cranial ischaemic complications of GCA, and 61.3% (N=1,182/1,929) had transient cranial ischaemic features **(Supplementary Table 4**). Furthermore, 14.0% (N=192/1,371) of the cohort had extra-cranial ischaemic features and 0.8% (N=11/1,630) had extra-cranial ischaemic complications. 33.3% (N=496/1,941) of the GCA cohort experienced PMR symptoms, with 33.3% (N=334/496) experiencing PMR symptoms before their GCA symptoms began, and 30.1% (N=162/539) experiencing an onset of PMR symptoms at the same time as their GCA symptoms. With regards to a systemic inflammatory response, 44.0% (N=352/800) of the cohort had ≥4kg of weight loss with the onset of GCA, whilst the median erythrocyte sedimentation rate (ESR) was 61 mm/h (IQR=34–89). Furthermore, the median C-reactive protein (CRP) of the cohort was 71 mg/L (IQR=17–106), and the median platelet count was 382 x 10^{-9}/L (IQR=286 to 455). Again, no considerable differences in clinical presentation were observed between diagnostic methods (including post-hoc analyses of 2022 ACR/EULAR classification criteria and the cohort with no confirmatory diagnostic test), and all subsequent analyses were performed on the total UK GCA cohort.

Supplementary Table 4. Patient clinical characteristics at presentation: total GCA cohort; those fulfilling imputed 1990 ACR classification criteria; fulfilling imputed 2022 ACR/EULAR classification criteria; confirmed diagnosis by temporal artery biopsy or vascular imaging; diagnosis not confirmed by biopsy or imaging.

	Total cohort (*N*=1,946)	Fulfilling imputed 1990 ACR classification criteria (*N*[1]=1,324/1,424)	Fulfilling imputed 2022 ACR/EULAR classification criteria* (*N*[1]=1,583/1,669)	Biopsy or imaging confirmed diagnosis (*N*[1]=992/1,434)	Diagnosis not confirmed by biopsy/imaging* (*N*[1]=442/1,434)
			MD (Q1 to Q3) or N (%)		
GCA symptoms to steroids duration (days)	45 (7 to 58)	44 (7 to 55)	45 (7 to 58)	48 (10 to 61)	42 (6 to 48)
Cranial ischaemic manifestations[2]					
Cranial ischaemic complications	327/1,925 (17.0%)	274/1321 (20.7%)	313/1576 (19.9%)	186/984 (18.9%)	67/438 (15.3%)
Ocular complications	297/1,922 (15.5%)	249/1310 (19.0%)	289/1566 (18.5%)	176/985 (17.9%)	58/438 (13.2%)
Non-ocular cranial complications	42/1,466 (2.9%)	34/1192 (2.9%)	36/1324 (2.7%)	14/745 (1.9%)	14/343 (4.1%)
Transient cranial ischaemic features*	938/1,604 (58.5%)	601/1,043 (57.6%)	784/1262 (62.1%)	501/800 (62.6%)	208/372 (55.9%)
Ocular ischaemic features*	429/1,922 (22.3%)	244/1310 (18.6%)	313/1566 (20.0%)	217/985 (22.0%)	114/438 (26.0%)
Non-ocular cranial ischaemic features*	768/1,588 (48.4%)	491/1035 (47.4%)	675/1252 (53.9%)	436/798 (54.6%)	143/367 (39.0%)
Extra-cranial ischaemic manifestations					
Extra-cranial ischaemic features[3]	192/1,371 (14.0%)	148/1108 (13.4%)	173/1236 (14.0%)	95/707 (13.4%)	44/285 (15.44%)
Extra-cranial ischaemic complications[4]	11/1,630 (0.8%)	10/1225 (0.9%)	11/1407 (0.9%)	5/851 (0.7%)	0/340 (0%)
PMR and polymyalgic symptoms at presentation[5]	496/1,491 (33.3%)	363/1212 (36.0%)	457/1343 (34.0%)	239/775 (30.8%)	93/333 (27.93%)
Before GCA symptoms started	334/496 (67.3%)	203/363 (55.9%)	309/498 (62.1%)	149/239 (62.3%)	64/108 (59.26%)

At GCA presentation	162/496 (32.7%)	124/363 (34.2%)	41/498 (8.2%)	76/239 (31.8%)	29/108 (26.85%)
Systemic inflammatory Response					
Weight loss /kg	0.12 (-2.1 to 3.2)	0 (-2.3 to 3.2)	0.14 (-2 to 3.2)	0.5 (-1.9 to 3.3)	0 (–1.25 to 3)
Weight loss ≥ 4kg	352/800 (44.0%)	283/641 (44.2%)	322/719 (44.8%)	188/382 (49.2%)	66/182 (36.26%)
ESR, mm/h	61 (34 to 89)	66 (40 to 93)	62 (35 to 90)	65 (37 to 93)	61.72 (35 to 88)
CRP, mg/L	71 (17 to 106)	76 (21 to 113)	74 (20 to 109)	80 (24 to 116)	61.54 (9 to 97.5)
Platelet count, x 10^9/L	382 (286 to 455)	389 (290 to 462)	386 (288 to 460)	401 (304 to 480)	355.39 (271 to 422)

**Post-hoc analysis requested by reviewers.*

[1]*Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.*

[2]***Cranial ischaemic manifestations at giant cell arteritis (GCA) presentation**. **A) Transient cranial ischaemic features. Ocular ischaemic features**: transient diplopia (DIP); transient double vision/absence of ocular motility (TDV); transient field defect (TFD); transient reduced acuity (TRA); transient vision loss (TVL). **Non-ocular cranial ischaemic features**: jaw claudication; tongue claudication; transient ischaemic attack (TIA) at presentation considered secondary to GCA. **B) Cranial ischaemic complications**. **Ocular complications**: Anterior ischaemic optic neuropathy (AION); branch retinal artery occlusion (BRAO); cilioretinal artery occlusion (CAO); cranial nerve palsy (CNP: III, IV or V); central retinal artery occlusion (CRAO); posterior ischaemic optic neuropathy (PION); relative afferent pupillary defect (RAPD); irreversible visual loss (PVL); irreversible visual field defect (PVFD); irreversible ocular motility; irreversible diplopia. **Non-ocular cranial complications:** Scalp necrosis; tongue necrosis; cerebrovascular accident (CVA) at presentation considered secondary to GCA.*

[3]*Extra-cranial ischaemic features: Arm claudication; leg claudication*

[4]*Extra-cranial ischaemic complications: fixed vascular stenosis to limb at presentation, secondary to GCA*

[5]*Polymyalgia rheumatica (PMR) and polymyalgic symptoms: Polymyalgic symptoms and/or a formal PMR diagnosis were recorded at the time of initial GCA diagnosis. Where PMR was diagnosed and treated with medium-dose glucocorticoids (e.g. 10-20mg prednisolone) prior to developing symptoms of GCA we classified these cases as having PMR prior to GCA, whereas untreated symptoms at GCA presentation were recorded as occurring at GCA presentation.*

**Omitting individuals with cranial ischaemic complications.*

ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology; MD, median; Q, quartile; N, sample number; PMR, polymyalgia rheumatica; GCA, giant cell arteritis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Furthermore, of the GCA cohort, 23.3% (N=370/1,586) had a history of cardiovascular disease (CVD; consisting of angina, myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), transient ischaemic attack (TIA) or cerebrovascular accident (CVA) unrelated to GCA presentation, peripheral vascular disease (PVD), or aortic aneurysm), 43.8% (N=653/1,490) had hypertension, 27.7% had hyperlipidemia (N=430/1,550) and 14.0% (N=207/1,478) had diabetes **(Supplementary Table 5**). Additionally, 28.3% (N=373/1,319) of the cohort were prescribed cholesterol-lowering medication, of whom 64.1% (N=234/365) had known hyperlipidaemia, of whom 41.2% (N=152/369) had CVD and of whom 24.8% (N=91/367) had a prior CV event (MI, CVA). Finally, 17.4% (N=231/1,325) of the cohort were prescribed antiplatelet medication, 4.4% (N=62/1,402) were prescribed anticoagulant medication, and 1.4% (N=18/1306) were prescribed duel antiplatelet and anticoagulant medication at presentation. There were no notable differences in CVD features at presentation between diagnostic methods compared with the total GCA cohort.

Supplementary Table 5. Patient Cardiovascular-related characteristics at presentation: total GCA cohort; those fulfilling imputed 1990 ACR classification criteria; fulfilling imputed 2022 ACR/EULAR classification criteria; confirmed diagnosis by temporal artery biopsy or vascular imaging; diagnosis not confirmed by biopsy or imaging.

	Total cohort (*N*=1,946)	Fulfilling imputed 1990 ACR classification criteria (N^I= 1,324/1,424)	Fulfilling imputed 2022 ACR/EULAR classification criteria* (N^I=1,583/1,669)	Confirmed diagnosis (N^I=992/1,434)	Diagnosis not confirmed by biopsy/imaging$^{\pm}$ (N^I=442/1,434)
			MD (Q1 to Q3) or N (%)		
CVD comorbidity composite*	370/1,586 (23.3%)	285/1281 (22.3%)	321/1421 (22.6%)	179/807 (22.2%)	84/364 (23.1%)
Component CVD comorbidities					
Angina	98/1,447 (6.8%)	79/1171 (6.8%)	85/1300 (6.5%)	42/749 (5.6%)	28/296 (9.5%)
Myocardial infarction	75/1,480 (5.1%)	63/1200 (5.3%)	69/1331 (5.2%)	36/766 (4.7%)	16/305 (5.3%)
Atrial fibrillation	104/1,209 (8.6%)	77/954 (8.1%)	91/1078 (8.4%)	55/599 (9.2%)	18/262 (6.9%)
Heart failure	22/1,201 (1.8%)	17/950 (1.8%)	18/1072 (1.7%)	9/592 (1.5%)	5/262 (1.9%)
TIA/CVA	119/1,476 (8.1%)	95/1195 (8.0%)	103/1327 (7.8%)	54/764 (7.1%)	26/304 (8.6%)
Peripheral vascular disease	42/1,472 (2.9%)	31/1192 (2.6%)	34/1323 (2.6%)	24/759 (3.2%)	3/305 (1.0%)
Aortic Aneurysm	23/1,451 (1.6%)	16/1163 (1.4%)	34/1323 (2.57%)	8/720 (1.1%)	9/348 (2.6%)
CV risk factors					
Diabetes	207/1,478 (14.0%)	156/1195 (13.1%)	184/1331 (13.8%)	89/766 (11.6%)	57/307 (18.6%)
Hyperlipidaemia	430/1,550 (27.7%)	342/1251 (27.3%)	387/1392 (27.8%)	189/785 (24.1%)	120/359 (33.4%)
Hypertension	653/1,490 (43.8%)	527/1205 (43.7%)	588/1341 (43.9%)	322/771 (41.8%)	146/309 (47.3%)
CVD medications					

Antiplatelet therapy	231/1,325 (17.4%)	186/1084 (17.2%)	208/1200 (17.3%)	109/691 (15.8%)	56/279 (20.1%)
Anticoagulant therapy	62/1,402 (4.4%)	46/1144 (4.0%)	54/1266 (4.3%)	28/726 (3.9%)	14/297 (4.7%)
Cholesterol-lowering medication	373/1,319 (28.3%)	307/1091 (28.1%)	341/1196 (28.5%)	165/669 (24.7%)	92/303 (30.4%)

[±]*Post-hoc analysis requested by reviewers.*
[1]*Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.*

**Consisting of angina, myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), transient ischaemic attack (TIA) or cerebrovascular accident (CVA) unrelated to GCA presentation, peripheral vascular disease (PVD), or aortic aneurysm*

ACR, American college of rheumatology; EULAR, European Alliance of Associations for Rheumatology; MD, median; Q, quartile; N, sample number; TIA, transient ischaemic attack; CVA, cerebrovascular accident.

Descriptive statistics of cohort with ischaemic features

Of the cohort with the primary outcome, 27.2% (N=86/316) had CVD (in the CVD comorbidity composite), 51.2% (N=151/295) had hypertension and 15.6% (N=46/295) had diabetes mellitus (**65**). Finally, 33.7% (N=88/261) of the cohort were taking cholesterol-lowering medication, 21.8% (N=57/261) of the cohort were taking antiplatelet medication, and 2.5% (N=7/280) were taking anticoagulant medication.

Supplementary Table 6. Patient Cardiovascular-related characteristics at presentation: cranial ischaemic complications; transient cranial ischaemic manifestations; non-cranial ischaemic features.

	Cranial ischaemic complications (N^1=327/1,925)	Transient cranial ischaemic manifestations± (N^1=951/1,604)	Non-cranial ischaemic features (N^1=203/1630)	No ischaemic features (N^1=514/1,944)
	MD (Q1 to Q3) or N (%)			
CVD comorbidity composite*	86/316 (27.2%)	155/700 (22.1%)	56/197 (28.4%)	88/472 (18.6%)
Component CVD comorbidities				
Angina	24/285 (8.4%)	38/622 (6.1%)	15/185 (8.1%)	30/465 (6.5%)
Myocardial infarction	15/292 (5.1%)	36/641 (5.6%)	17/194 (8.8%)	17/468 (3.6%)
Atrial fibrillation	20/227 (8.8%)	39/491 (7.9%)	10/151 (6.6%)	36/425 (8.5%)
Heart failure	4/225 (1.8%)	8/486 (1.7%)	3/146 (2.1%)	7/425 (1.7%)
TIA/CVA	32/287 (11.2%)	54/643 (8.4%)	17/192 (8.9%)	29/467 (6.2%)
Peripheral vascular disease	11/288 (3.8%)	22/639 (3.4%)	15/194 (7.7%)	5/466 (1.1%)
Aortic Aneurysm	4/292 (1.4%)	9/634 (1.4%)	1/180 (0.6%)	9/441 (2.0%)
CV risk factors				
Diabetes	46/295 (15.6%)	82/638 (12.9%)	28/196 (14.3%)	63/469 (13.4%)
Hyperlipidaemia	108/312 (34.6%)	184/683 (26.9%)	70/190 (36.8%)	116/465 (25.0%)
Hypertension	151/295 (51.2%)	276/645 (42.8%)	94/196 (48.0%)	197/473 (41.7%)
CVD medications				
Antiplatelet therapy	57/261 (21.8%)	95/586 (16.2%)	29/178 (16.3%)	62/406 (15.3%)
Anticoagulant therapy	7/280 (2.5%)	23/611 (3.8%)	6/188 (3.2%)	29/435 (6.7%)
Cholesterol-lowering medication	88/261 (33.7%)	158/592 (26.7%)	52/172 (30.2%)	111/394 (28.2%)

[1]*Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.*

**Consisting of angina, myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), transient ischaemic attack (TIA) or cerebrovascular accident (CVA) unrelated to GCA presentation, peripheral vascular disease (PVD), or aortic aneurysm*

[±]*Omitting individuals with cranial ischaemic complications.*

MD, median; Q, quartile; N, sample number; TIA, transient ischaemic attack; CVA, cerebrovascular accident.

Descriptive statistics of cohort with cardiovascular comorbidities

370/1,586 (23.3%) UK GCA Consortium individuals in this study had one or more CV comorbidity. These CVD comorbidities were combined into a CVD composite (CVD; consisting of angina, myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), transient ischaemic attack (TIA) or cerebrovascular accident (CVA) unrelated to GCA presentation, peripheral vascular disease (PVD), or aortic aneurysm). Of these individuals, 64.0% (*N*=236/369) were female, and the median age of the cohort with the primary outcome (cranial ischaemic complications) at diagnosis was 72 (IQR = 67–78) years (**Supplementary Table 7**). 98.6% (*N*=353/358) of these individuals were "white European", 1.2% (*N*=3/242) had an "underweight" BMI of <18.5kg/m2, and 19.8% (*N*=48/242) had an "obese" BMI of ≥ 30kg/m^2. 8.2% (N=23/282) of these individuals consumed ≥ 14 units of alcohol per week (with the average number of alcohol units consumed per week being 4.2 [IQR=0–6]) and 14.2% (N=50/353) smoked tobacco at GCA diagnosis. This cohort had a slightly smaller proportion of females than the total cohort (64.0% and 68.7%, respectively). Otherwise, no considerable differences were observed between this cohort and the total GCA cohort.

Supplementary Table 7. Patient demographics at presentation: cardiovascular comorbidities; cardiovascular risk factors; hypertension; diabetes; antiplatelet/anticoagulant therapy; cholesterol-lowering therapy/hyperlipidemia.

	Cardiovascular disease* (N^1=370/1,586)	Hypertension (N^1=653/1,490)	Diabetes (N^1=156/1195)	Antiplatelet /anticoagulant drugs (N^1=219/1071)	Cholesterol-lowering drugs and/or hyperlipidemia (N^1=569/1595)
			MD (Q1 to Q3) or N (%)		
Age at diagnosis (years)	72 (67 to 78)	72 (67 to 78)	71 (66 to 77)	73 (69 to 78)	72 (67 to 77)
Sex (female)	236/369 (64.0%)	443/651 (68.1%)	120/206 (58.3%)	166/274 (60.6%)	361/566 (63.8%)
Ethnicity					
EUR	353/358 (98.6%)	627/636 (98.6%)	187/196 (95.4%)	261/263 (99.2%)	538/546 (98.5%)
AFR	1/358 (0.3%)	2/636 (0.3%)	2/196 (1.0%)	0/263 (0%)	1/546 (0.2%)
SAS	4/358 (1.1%)	7/636 (1.1%)	7/196 (3.6%)	2/263 (0.8%)	7/546 (1.3%)
EAS	0/358 (0%)	0/636 (0%)	0/196 (0%)	0/263 (0%)	0/546 (0%)
Family history of GCA	3/230 (1.3%)	15/409 (3.7%)	4/123 (3.3%)	3/183 (1.6%)	13/352 (3.7%)
Family history of PMR	7/229 (3.1%)	19/407 (4.7%)	4/122 (3.3%)	7/182 (3.9%)	16/348 (4.6%)
BMI (kg/m^2)					
<18.5	3/242 (1.2%)	4/403 (1.0%)	0/127 (0%)	2/180 (1.1%)	3/347 (0.9%)
18.5 to <25	90/242 (37.2%)	138/403 (34.2%)	32/127 (25.2%)	70/180 (38.9%)	134/347 (38.6%)
25 to <30	101/242 (41.7%)	170/403 (42.2%)	54/127 (42.5%)	72/180 (40.0%)	136/347 (39.2%)
≥ 30 kg/m^2	48/242 (19.8%)	91/403 (22.6%)	41/127 (32.3%)	36/180 (20%)	74/347 (21.3%)
Smoking tobacco (ever)	188/353 (53.3%)	328/632 (51.9%)	104/194 (53.6%)	145/263 (55.1%)	292/553 (52.8%)
Smoking tobacco at GCA diagnosis	50/353 (14.2%)	63/632 (10.0%)	24/193 (12.4%)	27/263 (10.3%)	71/552 (12.9%)
Alcohol units/week	4.20 (0 to 6.00)	4.90 (0 to 6.00)	3.20 (0 to 3.00)	5.06 (0 to 7.00)	5.05 (0 to 7.00)
Alcohol ≥ 14 units/week	23/282 (8.2%)	50/508 (9.8%)	10/155 (6.5%)	20/202 (9.9%)	46/419 (11.0%)
Index of Multiple Deprivation					

2019 (quintiles)					
1 (most deprived)	52/251 (20.7%)	100/468 (21.4%)	42/140 (30.0%)	45/196 (23.0%)	85/383 (22.2%)
2	56/251 (22.3%)	89/468 (19.0%)	28/140 (20.0%)	41/196 (20.9%)	81/383 (21.2%)
3	53/251 (21.1%)	92/468 (19.7%)	24/140 (17.1%)	31/196 (15.8%)	68/383 (17.8%)
4	58/251 (23.1%)	114/468 (24.4%)	23/140 (16.4%)	43/196 (21.9%)	75/383 (19.6%)
5 (least deprived)	32/251 (12.8%)	73/468 (15.6%)	23/140 (16.4%)	36/196 (18.4%)	74/383 (19.3%)

[1]*Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.*

**Consisting of angina, myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), transient ischaemic attack (TIA) or cerebrovascular accident (CVA) unrelated to GCA presentation, peripheral vascular disease (PVD), or aortic aneurysm.*

MD, median; Q, quartile; N, sample number; EUR, white European (European/American); AFR, African; EAS, east Asian; SAS, south Asian; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; CV, cardiovascular disease; BMI, body mass index.

Of the cohort with CVD, 23.3% (N=86/369) had cranial ischaemic complications in GCA, whilst 61.0% (N=222/364) had transient cranial ischaemic features, 17.0% (N=53/314) had extracranial ischaemic features and 1.0% (N=3/351) had extra-cranial ischaemic complications (**Supplementary Table 8**). 34.4% (N=114/331) of these individuals had PMR symptoms, and 72.8% (N=83/114) of those with PMR symptoms experienced these before their GCA symptoms began. Furthermore, 45.8% (N=98/214) of the CVD group had weight loss of ≥4kg at the onset of GCA, the median ESR was 58 mm/h (IQR=32–82), the median CRP was 70 mg/L (IQR=13–100), and the median platelet count of the cohort was 369 x 10^{9}/L (IQR=273 to 439).

Supplementary Table 8. Patient clinical characteristics at presentation: cardiovascular disease composite; hypertension; diabetes; antiplatelet/anticoagulant therapy; cholesterol lowering therapy/hyperlipidemia.

	Cardiovascular disease* (N[1]=370/1,586)	Hypertension (N[1]=653/1,490)	Diabetes (N[1]=156/1195)	Antiplatelet/anticoagulant drugs (N[1]=219/1071)	Cholesterol lowering drugs/hyperlipidemia (N[1]=569/1595)
	MD (Q1 to Q3) or N (%)				
GCA symptoms to steroids duration (days)	48 (7 to 59)	47 (7 to 56)	34 (5 to 43)	44 (8 to 55)	49 (7 to 59)
Cranial ischaemic complications	86/369 (23.3%)	151/651 (23.2%)	46/204 (22.6%)	61/275 (22.2%)	136/569 (24.0%)
Ocular complications	79/366 (21.6%)	138/645 (21.4%)	44/203 (21.7%)	57/274 (20.8%)	99/453 (21.9%)
Non-ocular cranial complications	11/328 (3.4%)	18/585 (3.1%)	3/177 (1.7%)	6/250 (2.4%)	19/512 (3.7%)
Transient cranial ischaemic features[±]	154/279 (55.2%)	275/497 (55.3%)	80/157 (51.0%)	112/211 (53.1%)	247/431 (57.3%)
Ocular ischaemic features[±]	61/366 (16.7%)	112/645 (17.4%)	31/203 (15.3%)	49/274 (17.9%)	90/453 (19.9%)
Non-ocular cranial ischaemic features[±]	126/276 (45.7%)	222/495 (44.9%)	67/155 (43.2%)	90/210 (42.9%)	195/426 (45.8%)
Extra-cranial ischaemic features[3]	53/314 (16.9%)	89/574 (15.5%)	26/183 (14.2%)	33/247 (13.4%)	80/498 (16.1%)
Extra-cranial ischaemic complications[4]	3/351 (1.0%)	5/639 (0.9%)	2/200 (1.1%)	1/268 (0.4%)	6/546 (1.2%)
PMR symptoms at presentation					
PMR symptoms	114/331 (34.4%)	195/589 (33.1%)	63/181 (34.8%)	72/257 (28.0%)	132/413 (32.0%)
Before GCA symptoms started	83/114 (72.8%)	131/195 (67.2%)	46/63 (73.0%)	51/72 (70.9%)	116/168 (69.1%)
Same time as GCA symptoms	31/114 (27.2%)	64/195 (32.8%)	17/63 (27.0%)	21/72 (29.2%)	52/168 (31.0%)
Weight loss /kg	0.61 (-1.00 to 4.00)	-0.01 (-3.00 to 3.70)	0.59 (-0.40 to 4.00)	0.30 (-1.10 to 3.20)	0.18 (-1.40 to 3.20)
Weight loss ≥ 4kg	98/214 (45.8%)	170/348 (48.9%)	49/100 (49%)	66/155 (42.6%)	136/310 (43.9%)

ESR mm/h	58	62	60	60	60
	(32 to 82)	(36 to 90)	(33 to 87)	(33 to 86)	(34 to 88)
CRP mg/L	70	70	74	70	69
	(13 to 100)	(19 to 104)	(12 to 111)	(19 to 99)	(13 to 100)
Platelet count	369	380	355	364	372
x 10*9/L	(273 to 439)	(287 to 447)	(266 to 420)	(272 to 425)	(280 to 446)

[1]*Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.*

[2]***Cranial ischaemic manifestations**. **A) Transient cranial ischaemic features. Ocular ischaemic features**: transient diplopia (DIP); transient double vision/absence of ocular motility (TDV); transient field defect (TFD); transient reduced acuity (TRA); transient vision loss (TVL). **Non-ocular cranial ischaemic features**: jaw claudication; tongue claudication; transient ischaemic attack (TIA) at presentation considered secondary to GCA. **B) Cranial ischaemic complications**. **Ocular complications**: Anterior ischaemic optic neuropathy (AION); branch retinal artery occlusion (BRAO); cilioretinal artery occlusion (CAO); cranial nerve palsy (CNP: III, IV or V); central retinal artery occlusion (CRAO); posterior ischaemic optic neuropathy (PION); relative afferent pupillary defect (RAPD); irreversible visual loss (PVL); irreversible visual field defect (PVFD); irreversible ocular motility; irreversible diplopia. **Non-ocular cranial complications:** Scalp necrosis; tongue necrosis; cerebrovascular accident (CVA) at presentation considered secondary to GCA.*

[3]*Extra-cranial ischaemic features: Arm claudication; leg claudication*

[4]*Extra-cranial ischaemic complications: fixed vascular stenosis to limb at presentation, secondary to GCA*

[±]*Omitting individuals with cranial ischaemic complications.*

**Consisting of angina, myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), transient ischaemic attack (TIA) or cerebrovascular accident (CVA) unrelated to GCA presentation, peripheral vascular disease (PVD), or aortic aneurysm*

MD, median; Q, quartile; N, sample number; PMR, polymyalgia rheumatica; GCA, giant cell arteritis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Finally, of the cohort with CVDs, 56.3% (N=205/364) also had hypertension and 19.4% (N=70/360) had diabetes (**Supplementary Table 9**). In addition to this, 51.0% (N=152/298) of the cohort were taking cholesterol-lowering medication, 37.5% (N=122/325) of the cohort were taking antiplatelet medication, and 15.3% (N=51/334) were taking anticoagulant medication.

Supplementary Table 9. Patient CV-related characteristics at presentation: cardiovascular disease composite; hypertension; diabetes; antiplatelet/anticoagulant therapy; cholesterol lowering therapy/hyperlipidemia.

	Cardiovascular disease* (N[1]=370/1,586)	Hypertension (N[1]=653/1,490)	Diabetes (N[1]=156/1195)	Antiplatelet/anticoagulant drugs (N[1]=219/1071)	Cholesterol lowering drugs and/or hyperlipidemia (N[1]=569/1595)
	MD (Q1 to Q3) or N (%)				
CVD comorbidity composite*	370/370 (100.0%)	205/645 (31.8%)	70/205 (34.2%)	158/270 (58.5%)	209/562 (37.2%)
Component CVD comorbidities					
Angina	98/359 (27.3%)	60/624 (9.6%)	20/201 (10.0%)	53/255 (20.8%)	67/535 (12.5%)
Myocardial infarction	75/363 (20.7%)	47/640 (7.3%)	20/204 (10.0%)	38/267 (14.2%)	57/547 (10.4%)
Atrial fibrillation	104/309 (33.7%)	58/520 (11.2%)	19/173 (11.0%)	47/225 (20.9%)	49/441 (11.1%)
Heart failure	22/305 (7.2%)	14/516 (2.7%)	6/170 (3.5%)	8/221 (3.6%)	11/438 (2.5%)
TIA/CVA	119/362 (32.9%)	62/636 (9.8%)	24/202 (11.9%)	49/265 (18.5%)	75/544 (13.8%)
Peripheral vascular disease	42/360 (11.7%)	23/635 (3.6%)	7/205 (3.4%)	13/264 (4.9%)	23/543 (4.2%)
Aortic Aneurysm	23/339 (6.8%)	10/589 (1.7%)	4/190 (2.1%)	7/244 (2.9%)	7/514 (1.4%)
CV risk factors					
Diabetes	70/360 (19.4%)	123/641 (19.2%)	207/207 (100.0%)	53/266 (19.9%)	132/550 (24.0%)
Hyperlipidaemia	136/361 (37.7%)	261/634 (41.2%)	95/202 (47.0%)	107/262 (40.8%)	430/561 (76.7%)
Hypertension	205/364 (56.3%)	653/653 (100.0%)	123/207 (59.4%)	163/270 (60.4%)	335/554 (60.5%)
CVD medications					
Antiplatelet therapy	122/325 (37.5%)	139/559 (24.9%)	45/171 (26.3%)	231/275 (84.0%)	160/486 (32.9%)
Anticoagulant therapy	51/334 (15.3%)	35/601 (5.8%)	12/188 (6.4%)	62/275 (22.6%)	33/520 (6.4%)
Cholesterol-lowering medication	152/298 (51.0%)	227/541 (42.0%)	86/162 (53.1%)	159/242 (65.7%)	373/504 (74.0%)

[1]*Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.*

**Consisting of angina, myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), transient ischaemic attack (TIA) or cerebrovascular accident (CVA) unrelated to GCA presentation, peripheral vascular disease (PVD), or aortic aneurysm*

ACR, American college of rheumatology; MD, median; Q, quartile; N, sample number; TIA, transient ischaemic attack; CVA, cerebrovascular accident.

Correlations between cardiovascular variables

Pairwise correlations between risk factors investigated in this work were assessed using Pearson's correlation coefficient. No pairs of variables had a correlation coefficient $R^2 \geq 0.80$ (**Supplementary Table 10**). However, a small number of variables had a degree of correlation ($R^2 \geq 0.45$), including: CRP and ESR (R^2=0.50, P=1.28 x 10^{-69}), anticoagulant therapy and AF (R^2=0.49, P=4.75 x 10^{-66}), and cholesterol-lowering medication and hyperlipidemia (R^2=0.50, P=3.44 x 10^{-80}). There were also correlations with $R^2 \geq 0.45$ between several CV-related PRS, including: body fat percentage PRS and BMI PRS (R^2=0.45, P=8.02 x 10^{-91}), weight PRS and BMI PRS (R^2=0.52, P=3.45 x 10^{-126}), weight PRS and basal metabolic rate (BMR) PRS (R^2=0.63, P=1.01 x 10^{-203}), and hyperlipidemia PRS and LDL PRS (R^2=0.52, P=1.54 x 10^{-127}).

Multivariable associations with cranial ischaemic complications in GCA

The GCA dataset was reduced to include only cases with non-missing values for all clinical and sociodemographic variables with univariable association LR P-values ≤ 0.10 (**Supplementary Tables 11 to 13**). This resulted in a dataset of 789 cases, which were split into a training and testing set using a 70:30 ratio (training N=552, testing N=237) to optimize the elastic net regression model **(Supplementary Table 14)**, resulting in an α parameter of 0.50 and a λ of 8.85 x 10^{-3}.

Supplementary Table 11. Univariate associations between demographic factors and cranial ischaemic complications.

	Primary Univariate Associations			Sensitivity analyses[1]		
Trait	**OR (95%CIs)**	***P*-value***	**DF**	**OR (95%CIs)**	***P*-value***	**DF**
Age at GCA diagnosis[±]		2.00×10^{-3}	1899		1.00×10^{-3}	909
< 60 years	1.00			1.00		
60 to < 70 years	0.99 (0.57 to 1.71)			0.95 (0.52 to 1.74)		
70 to < 80 years	1.43 (0.84 to 2.43)			1.63 (0.91 to 2.92)		
≥ 80 years	1.54 (0.87 to 2.74)			1.66 (0.87 to 3.17)		
Sex	0.89 (0.69 to 1.14)	0.36	1918	0.99 (0.74 to 1.32)	0.95	923
Ethnicity		0.48	1858		0.32	898
AFR	1.00			1.00		
EUR	0.20 (0.01 to 3.28)			0 (0 to Inf)		
SAS	0.30 (0.01 to 6.38)			0 (0 to Inf)		
BMI ±	1.00	0.35	934	1.00	0.63	512
<18.5	1 (0.59 to 1.70)			0.91 (0.50 to 1.65)		
18.5 to <25	0.93 (0.54 to 1.59)			0.92 (0.51 to 1.69)		
25 to <30	1.04 (0.62 to 1.77)			0.75 (0.42 to 1.34)		
≥ 30 kg/m^2	1.19 (0.71 to 2.00)			0.99 (0.55 to 1.76)		
Smoking tobacco at GCA diagnosis	0.98 (0.68 to 1.42)	0.92	1557	1.01 (0.66 to 1.53)	0.97	805
Alcohol units/week		0.21	1188		0.39	631
0	1.00			1.00		
≥ 1 to < 7	0.85 (0.61 to 1.19)			0.84 (0.57 to 1.22)		
≥ 7 to < 94.5	0.86 (0.59 to 1.26)			0.98 (0.63 to 1.51)		
Index of Multiple Deprivation 2019 (quintiles)		0.55	1329		0.41	615
1 (most deprived)	1.00			1.00		
2	1.00 (0.63 to 1.58)			0.90 (0.53 to 1.51)		
3	0.74 (0.46 to 1.2)			0.70 (0.41 to 1.21)		
4	1.13 (0.72 to 1.77)			1.20 (0.72 to 2.01)		
5 (least deprived)	0.84 (0.53 to 1.35)			0.70 (0.41 to 1.20)		

[1]*Sensitivty analyses including a reference group with no ischaemic features.*

[*]*P-value from likelihood ratio test.*

[±]*Analyses performed using continuous variables, quantile/group odds ratios presented for interpretation purposes.*

OR, odds ratio; CI, confidence interval; DF, degrees of freedom; GCA, giant cell arteritis; BMI, body mass index; AFR, African; EUR, European; SAS, south Asian; SES, socio-economic status.

Supplementary Table 12. Univariate associations between clinical/systemic inflammatory syndrome factors and cranial ischaemic complications.

	Primary Univariate Associations			Sensitivity analyses[1]		
Trait	**OR (95%CIs)**	***P*-value***	**DF**	**OR (95%CIs)**	***P*-value***	**DF**
Symptoms to steroid duration	1.00 (1.00 to 1.00)	0.68	1191	1.00 (1.00 to 1.00)	0.27	631
PMR symptoms	0.73 (0.56 to 0.95)	0.02	1529	0.86 (0.64 to 1.17)	0.33	789
Onset of PMR symptoms	0.69 (0.40 to 1.18)	0.17	493	0.92 (0.50 to 1.7)	0.80	229
Weight loss [kg] quintiles±		0.24	680		0.26	215
< -3.5	1.00			1.00		
-3.5 to < 0	0.57 (0.27 to 1.19)			0.53 (0.24 to 1.18)		
0 to < 1	1.24 (0.70 to 2.19)			1.33 (0.7 to 2.53)		
1 to < 4.1	0.87 (0.47 to 1.63)			0.85 (0.43 to 1.69)		
≥ 4.1	1.23 (0.68 to 2.23)			1.36 (0.70 to 2.66)		
Weight loss [≥ 4kg]	1.54 (1.08 to 2.19)	0.02	797	1.85 (1.24 to 2.75)	2.00×10^{-3}	437
ESR [mm/h] quintiles±		0.09	1200		0.57	654
< 29	1.00			1.00		
29 to < 49	0.57 (0.36 to 0.91)			0.60 (0.36 to 1.00)		
49 to < 69	1.08 (0.71 to 1.64)			1.29 (0.80 to 2.08)		
69 to <96	0.69 (0.44 to 1.08)			0.76 (0.46 to 1.26)		
≥ 96	0.67 (0.43 to 1.04)			0.82 (0.50 to 1.34)		
CRP [mg/L] quintiles±		0.34	1371		0.82	720
< 12	1.00			1.00		
12 to < 36	0.86 (0.57 to 1.29)			0.85 (0.54 to 1.35)		
36 to < 67.72	0.65 (0.42 to 1.00)			0.67 (0.42 to 1.09)		
67.72 to < 120	0.81 (0.54 to 1.23)			1.00 (0.62 to 1.60)		
≥ 120	0.79 (0.52 to 1.20)			0.97 (0.61 to 1.56)		
Platelets [x109/L] quintiles±		0.06	1507		0.69	770
< 271	1.00			1.00		
271 to < 334.8	0.65 (0.44 to 0.96)			0.78 (0.50 to 1.22)		
334.8 to < 396	0.67 (0.45 to 0.99)			0.81 (0.52 to 1.27)		
396 to < 485	0.89 (0.61 to 1.29)			1.20 (0.78 to 1.84)		
≥ 485	0.61 (0.41 to 0.91)			0.90 (0.57 to 1.42)		

[1]*Sensitivty analyses including a reference group with no ischaemic features.*

[*]*P-value from likelihood ratio test.*

[±]*Analyses performed using continuous variables, quantile/group odds ratios presented for interpretation purposes.*

OR, odds ratio; CI, confidence interval; DF, degrees of freedom; PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Supplementary Table 13. Univariate associations between CV-related factors and cranial ischaemic complications.

	Primary Univariate Associations			Sensitivity analyses[1]		
Trait	**OR (95%CIs)**	***P*-value^**	**DF**	**OR (95%CIs)**	***P*-value^**	**DF**
CVD comorbidity composite*	1.68 (1.27 to 2.22)	$< 1.00 \times 10^{-3}$	1924	1.52 (1.11 to 2.10)	0.01	930
Component CVD comorbidities						
Angina	1.36 (0.84 to 2.20)	0.21	1527	1.31 (0.76 to 2.29)	0.34	803
Myocardial infarction	1.01 (0.56 to 1.80)	0.92	1568	1.38 (0.68 to 2.78)	0.42	815
Atrial fibrillation	1.02 (0.61 to 1.70)	0.94	1293	0.92 (0.53 to 1.62)	0.78	699
Heart failure	0.95 (0.32 to 2.82)	0.92	1289	0.74 (0.23 to 2.39)	0.61	700
TIA/CVA	1.64 (1.06 to 2.52)	0.03	1550	1.78 (1.06 to 2.99)	0.03	801
Peripheral vascular disease	1.46 (0.72 to 2.93)	0.31	1558	3.08 (1.13 to 8.42)	0.02	811
Aortic Aneurysm	0.83 (0.28 to 2.46)	0.73	1447	0.71 (0.22 to 2.34)	0.57	761
CV risk factors						
Diabetes	1.19 (0.83 to 1.70)	0.35	1545	1.09 (0.73 to 1.63)	0.67	809
Hyperlipidaemia	1.50 (1.15 to 1.96)	3.00×10^{-3}	1545	1.62 (1.19 to 2.21)	2.00×10^{-3}	810
Hypertension	1.59 (1.24 to 2.05)	$< 1.00 \times 10^{-3}$	1616	1.53 (1.15 to 2.03)	4.00×10^{-3}	827
CVD medications						
Antiplatelet therapy	1.42 (1.02 to 1.99)	0.04	1321	1.48 (1.00 to 2.20)	0.05	682
Anticoagulant therapy	0.50 (0.22 to 1.10)	0.06	1398	0.38 (0.16 to 0.87)	0.01	733
Antiplatelet/anticoagulant therapy	1.19 (0.86 to 1.65)	0.29	1302	1.16 (0.80 to 1.68)	0.44	676
Cholesterol-lowering medication	1.38 (1.03 to 1.84)	0.03	1316	1.38 (0.99 to 1.93)	0.06	678

1Sensitivty analyses including a reference group with no ischaemic features.

^P-value from likelihood ratio test.

***Consisting of angina, myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), transient ischaemic attack (TIA) or cerebrovascular accident (CVA) unrelated to GCA presentation, peripheral vascular disease (PVD), or aortic aneurysm*

±Analyses performed using continuous variables, quantile/group odds ratios presented for interpretation purposes.

OR, odds ratio; CI, confidence interval; DF, degrees of freedom; CVD, cardiovascular disease; TIA, transient ischaemic attacks; CVA, cerebrovascular accident

Supplementary Table 14. Weighting of variables in elastic net regression model

Trait	Weight
Age at diagnosis	5.55×10^{-3}
PMR	-0.04
ESR	-4.75×10^{-4}
Platelet count	-3.48×10^{-5}
CVD composite	0.05
TIA/CVA	0.03
Hyperlipidemia	0.05
Hypertension	0.05
Antiplatelet therapy	0.02
Anticoagulant therapy	-0.20
Cholesterol-lowering therapy	-0.05

PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CVD, cardiovascular disease; TIA, transient ischaemic attacks; CVA, cerebrovascular accident; PRS, polygenic risk score.

Elastic net regression with polygenic risk scores integrated

PRS with univariable association LR P-values ≤ 0.10 **(Supplementary Table 15)** were added to the clinical and sociodemographic model, and elastic net regression was used to perform variable selection. Samples with non-missing values for all variables were split into a training and testing set in a 70:30 ratio (training *N*=537, testing *N*=231) to optimize the model, resulting in an α parameter of 0.5 and a λ of 6.43×10^{-3}. Elastic net retained 12 variables (**Supplementary Table 16**), which were included in a multivariable regression model.

Supplementary Table 15. Univariate associations between polygenic risk scores and cranial ischaemic complications.

		Primary Univariate Associations			Sensitivity analyses[1]		
Trait		**OR (95%CIs)**	***P*-value***	**DF**	**OR (95%CIs)**	***P*-value***	**DF**
Body mass index PRS quintiles			0.79	1843		0.88	891
	1	1.00			1.00		
	2	1.14 (0.80 to 1.64)			1.13 (0.75 to 1.71)		
	3	1.24 (0.85 to 1.80)			1.14 (0.75 to 1.74)		
	4	0.97 (0.66 to 1.44)			0.87 (0.56 to 1.34)		
	5	0.96 (0.65 to 1.42)			1.05 (0.67 to 1.63)		
Waist-hip ratio PRS quintiles			0.53	1843		0.38	891
	1	1.00			1.00		
	2	0.95 (0.64 to 1.40)			0.87 (0.56 to 1.35)		
	3	0.84 (0.57 to 1.23)			0.86 (0.55 to 1.33)		
	4	1.15 (0.80 to 1.66)			1.05 (0.70 to 1.60)		
	5	0.88 (0.60 to 1.29)			0.84 (0.55 to 1.28)		
Basal metabolic rate PRS quintiles			0.89	1843		0.88	891
	1	1.00			1.00		
	2	0.71 (0.49 to 1.05)			0.68 (0.44 to 1.05)		
	3	0.96 (0.66 to 1.40)			0.94 (0.62 to 1.44)		
	4	0.85 (0.59 to 1.24)			0.86 (0.57 to 1.31)		
	5	0.92 (0.63 to 1.33)			0.97 (0.63 to 1.50)		
Body fat percentage PRS quintiles			0.50	1843		0.44	891
	1	1.00			1.00		
	2	1.68 (1.13 to 2.49)			1.33 (0.86 to 2.08)		
	3	1.25 (0.83 to 1.87)			1.01 (0.64 to 1.59)		
	4	1.27 (0.84 to 1.90)			1.08 (0.68 to 1.70)		
	5	1.37 (0.92 to 2.03)			1.37 (0.87 to 2.14)		
Platelets PRS quintiles			0.09	1843		0.17	891
	1	1.00			1.00		
	2	0.83 (0.57 to 1.21)			0.69 (0.45 to 1.06)		
	3	0.69 (0.47 to 1.03)			1.03 (0.68 to 1.56)		
	4	1.06 (0.73 to 1.54)			0.80 (0.53 to 1.21)		
	5	1.02 (0.7 to 1.48)			0.69 (0.45 to 1.06)		
C-reactive protein PRS quintiles			0.30	1843		0.34	891
	1	1.00			1.00		
	2	1.04 (0.71 to 1.54)			1.06 (0.68 to 1.65)		
	3	0.91 (0.61 to 1.36)			0.94 (0.60 to 1.49)		
	4	1.11 (0.75 to 1.63)			1.05 (0.68 to 1.63)		

	5	0.89 (0.59 to 1.32)			0.94 (0.60 to 1.48)		
Angina PRS quintiles			0.23	1843		0.29	891
	1	1.00			1.00		
	2	0.68 (0.47 to 0.99)			0.75 (0.49 to 1.14)		
	3	0.66 (0.45 to 0.96)			0.74 (0.48 to 1.14)		
	4	0.83 (0.58 to 1.19)			0.89 (0.59 to 1.34)		
	5	0.65 (0.44 to 0.95)			0.66 (0.43 to 1.02)		
Myocardial infarction PRS quintiles			0.54	1843		0.61	891
	1	1.00			1.00		
	2	1.02 (0.70 to 1.50)			0.99 (0.64 to 1.53)		
	3	1.17 (0.81 to 1.71)			1.07 (0.70 to 1.64)		
	4	0.88 (0.60 to 1.29)			0.73 (0.47 to 1.13)		
	5	0.90 (0.60 to 1.32)			0.93 (0.59 to 1.45)		
Atrial fibrillation PRS quintiles			0.50	1843		0.40	891
	1	1.00			1.00		
	2	0.84 (0.57 to 1.25)			0.84 (0.54 to 1.30)		
	3	1.04 (0.71 to 1.53)			1.25 (0.80 to 1.95)		
	4	0.98 (0.68 to 1.43)			0.94 (0.62 to 1.44)		
	5	0.77 (0.52 to 1.14)			0.75 (0.48 to 1.16)		
Heart failure PRS quintiles			0.40	1843		0.41	891
	1	1.00			1.00		
	2	1.20 (0.83 to 1.73)			1.16 (0.76 to 1.77)		
	3	1.03 (0.70 to 1.51)			0.97 (0.63 to 1.50)		
	4	0.72 (0.48 to 1.07)			0.71 (0.46 to 1.12)		
	5	0.99 (0.68 to 1.44)			0.97 (0.63 to 1.48)		
Transient ischaemic attacks PRS quintiles			0.03	1843		0.10	891
	1	1.00			1.00		
	2	0.98 (0.66 to 1.47)			0.75 (0.48 to 1.17)		
	3	1.25 (0.85 to 1.85)			1.03 (0.66 to 1.62)		
	4	0.97 (0.64 to 1.45)			0.78 (0.49 to 1.24)		
	5	1.37 (0.93 to 2.00)			1.22 (0.79 to 1.90)		
Stroke PRS quintiles			0.64	1843		0.91	891
	1	1.00			1.00		
	2	0.98 (0.68 to 1.42)			0.95 (0.62 to 1.44)		
	3	0.83 (0.56 to 1.22)			0.82 (0.53 to 1.27)		
	4	0.92 (0.63 to 1.34)			0.96 (0.62 to 1.47)		
	5	0.90 (0.62 to 1.32)			0.97 (0.63 to 1.49)		
Peripheral vascular disease PRS quintiles			0.61	1843		0.50	891
	1	1.00			1.00		
	2	0.83 (0.57 to 1.21)			0.81 (0.53 to 1.24)		

	3	0.69 (0.47 to 1.03)			0.72 (0.46 to 1.11)		
	4	1.06 (0.73 to 1.54)			1.07 (0.70 to 1.64)		
	5	1.02 (0.70 to 1.48)			1.03 (0.67 to 1.58)		
Abdominal aortic aneurysm PRS quintiles			0.81	1843		0.93	891
	1	1.00			1.00		
	2	1.09 (0.74 to 1.61)			1.17 (0.75 to 1.80)		
	3	1.27 (0.87 to 1.84)			1.37 (0.90 to 2.09)		
	4	1.29 (0.88 to 1.90)			1.42 (0.92 to 2.19)		
	5	1.02 (0.69 to 1.50)			1.08 (0.70 to 1.67)		
Thoracic aortic aneurysm PRS quintiles			0.20	1843		0.31	891
	1	1.00			1.00		
	2	1.32 (0.89 to 1.96)			1.20 (0.77 to 1.86)		
	3	1.38 (0.93 to 2.06)			1.37 (0.87 to 2.15)		
	4	1.42 (0.95 to 2.11)			1.29 (0.83 to 2.02)		
	5	1.29 (0.87 to 1.92)			1.23 (0.79 to 1.93)		
Thromboembolic disease quintiles			0.30	1843		0.31	891
	1	1.00			1.00		
	2	0.73 (0.49 to 1.1)			0.73 (0.47 to 1.15)		
	3	1.17 (0.81 to 1.71)			1.18 (0.77 to 1.81)		
	4	0.86 (0.59 to 1.26)			0.91 (0.59 to 1.40)		
	5	0.99 (0.68 to 1.45)			1.00 (0.65 to 1.53)		
Type 2 diabetes PRS quintiles			0.45	1843		0.13	891
	1	1.00			1.00		
	2	1.28 (0.85 to 1.91)			1.35 (0.87 to 2.11)		
	3	1.24 (0.82 to 1.87)			1.46 (0.92 to 2.31)		
	4	1.05 (0.70 to 1.58)			1.30 (0.82 to 2.04)		
	5	1.38 (0.93 to 2.04)			1.65 (1.06 to 2.56)		
Glycated haemoglobin PRS quintiles			0.29	1843		0.81	891
	1	1.00			1.00		
	2	1.10 (0.75 to 1.61)			1.08 (0.70 to 1.68)		
	3	0.91 (0.61 to 1.35)			0.85 (0.55 to 1.32)		
	4	1.00 (0.68 to 1.46)			1.05 (0.68 to 1.63)		
	5	0.92 (0.62 to 1.37)			0.93 (0.60 to 1.45)		
Hyperlipidemia PRS quintiles			0.31	1843		0.34	891
	1	1.00			1.00		
	2	1.01 (0.68 to 1.50)			0.98 (0.63 to 1.53)		
	3	1.13 (0.77 to 1.66)			1.25 (0.80 to 1.93)		
	4	0.80 (0.54 to 1.19)			0.83 (0.53 to 1.30)		
	5	0.83 (0.56 to 1.23)			0.84 (0.54 to 1.31)		

Triglycerides PRS quintiles			0.26	1843		0.68	891
	1	1.00			1.00		
	2	0.68 (0.47 to 0.99)			0.70 (0.46 to 1.07)		
	3	0.97 (0.68 to 1.39)			0.97 (0.65 to 1.46)		
	4	0.80 (0.55 to 1.17)			0.87 (0.57 to 1.33)		
	5	0.78 (0.53 to 1.13)			0.84 (0.55 to 1.28)		
Low density lipoprotein PRS quintiles			0.40	1843		0.61	891
	1	1.00			1.00		
	2	1.31 (0.88 to 1.94)			1.25 (0.80 to 1.95)		
	3	1.21 (0.81 to 1.79)			1.19 (0.76 to 1.86)		
	4	1.02 (0.68 to 1.51)			1.02 (0.64 to 1.57)		
	5	0.92 (0.62 to 1.38)			1.02 (0.65 to 1.61)		
High density lipoprotein PRS quintiles			0.19	1843		0.06	891
	1	1.00			1.00		
	2	0.74 (0.50 to 1.09)			0.76 (0.48 to 1.18)		
	3	0.69 (0.47 to 1.01)			0.71 (0.46 to 1.10)		
	4	0.75 (0.52 to 1.10)			0.72 (0.47 to 1.10)		
	5	0.73 (0.50 to 1.06)			0.68 (0.44 to 1.04)		
Hypertension PRS quintiles			0.66	1843		0.50	891
	1	1.00			1.00		
	2	1.31 (0.88 to 1.97)			1.42 (0.90 to 2.23)		
	3	1.21 (0.82 to 1.8)			1.40 (0.90 to 2.18)		
	4	1.32 (0.89 to 1.96)			1.46 (0.94 to 2.27)		
	5	1.19 (0.80 to 1.76)			1.29 (0.84 to 2.00)		

[1]*Sensitivty analyses including a reference group with no ischaemic features.*

[*]*P-value from likelihood ratio test.*

All analyses performed using continuous variables, quantile/group odds ratios presented for interpretation purposes.

OR, odds ratio; CI, confidence interval; DF, degrees of freedom; PRS, polygenic risk score.

Supplementary Table 16. Weighting of variables in elastic net regression model including PRS.

Trait	Weight
Age at diagnosis	4.82×10^{-3}
PMR	-0.03
ESR	-4.22×10^{-4}
Platelet count	0
CVD composite	0.04
TIA/CVA	0.01
Hyperlipidemia	0.04

Hypertension	0.04
Antiplatelet therapy	0.01
Anticoagulant therapy	-0.18
Cholesterol-lowering therapy	-0.03
Platelet count PRS	-0.02
TIA PRS	0.02

PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CVD, cardiovascular disease; TIA, transient ischaemic attacks; CVA, cerebrovascular accident; PRS, polygenic risk score.

Sex-Stratified multivariable associations with cranial ischaemic complications

In post-hoc analyses recommended by one of the reviewers we sought to determine whether there were sex-based differences in risk factors for cranial ischaemic complications. The model optimized for cranial ischaemic complications in GCA using elastic net regression was repeated in i) just males and ii) just females (**Supplementary Table 17**). There were a total of 262 males with complete data (58 with cranial ischaemic complications in GCA and 204 without), and a total of 550 females with complete data (110 with cranial ischaemic complications and 440 without). It was found that whilst both age at diagnosis (AOR[95% CI]=1.84 [0.72 to 4.99], *P*=0.01, for the highest [≥80 years] versus lowest [<60 years] decade) and anticoagulant use (AOR[95% CI]=0.17 [0.03 to 0.67], *P*=0.01) were strongly associated with cranial ischaemic complications in GCA in women, these variables were not strongly associated with cranial ischaemic complications in men.

Supplementary Table 17. Multivariable associations with cranial ischaemic complications in GCA at presentation, following variable selection with elastic net regression, stratified by sex.

	Male (*N*=262)		**Female (*N*=550)**	
Variable	**OR (95%CIs)**	***P-value****	**OR (95%CIs)**	***P-value****
Age at diagnosis[±]				
< 60 years	1.00	0.32	1.00	**0.01**
60 to < 70 years	0.76 (0.19 - 3.88)		0.48 (0.20 - 1.21)	
70 to < 80 years	1.11 (0.30 - 5.53)		1.01 (0.45 - 2.47)	
≥ 80 years	1.19 (0.26 - 6.74)		1.84 (0.72 - 4.99)	
PMR	1.00 (0.50 - 1.95)	0.99	0.74 (0.46 - 1.18)	0.17

ESR quintiles [mm/h] [±]				
< 29	1.00	0.14	1.00	0.42
29 to < 49	0.86 (0.31 - 2.41)		0.32 (0.14 - 0.70)	
49 to < 69	1.05 (0.39 - 2.82)		1.04 (0.52 - 2.08)	
69 to <96	0.52 (0.18 - 1.49)		0.59 (0.28 - 1.23)	
≥ 96	0.65 (0.23 - 1.80)		0.60 (0.29 - 1.21)	
CVD composite	0.73 (0.25 - 1.91)	0.45	1.46 (0.74 - 2.83)	0.28
TIA/CVA	3.90 (0.89 - 17.53)	0.07	0.92 (0.35 - 2.33)	0.89
Hyperlipidemia	0.87 (0.36 - 2.01)	0.48	1.85 (1.04 - 3.26)	0.12
Hypertension	1.67 (0.85 - 3.28)	0.16	1.27 (0.80 - 2.04)	0.28
Antiplatelet therapy	0.49 (0.17 - 1.33)	0.21	1.96 (1.02 - 3.72)	0.08
Anticoagulant therapy	0.19 (0.01 - 1.22)	0.11	0.17 (0.03 - 0.67)	**0.01**
Cholesterol-lowering therapy	1.27 (0.54 - 2.99)	0.59	0.48 (0.25 - 0.91)	0.07
Platelet count PRS quintiles[±]				
1	1.00	0.11	1.00	0.34
2	0.53 (0.2 - 1.35)		0.53 (0.25 - 1.07)	
3	0.64 (0.23 - 1.73)		1.33 (0.68 - 2.61)	
4	0.59 (0.22 - 1.53)		0.69 (0.35 - 1.34)	
5	0.32 (0.11 - 0.89)		0.54 (0.25 - 1.10)	
TIA PRS quintiles[±]				
1	1.00	0.17	1.00	0.40
2	1.81 (0.63 - 5.62)		0.65 (0.31 - 1.36)	
3	1.15 (0.35 - 3.85)		1.17 (0.58 - 2.36)	
4	1.92 (0.66 - 6.03)		0.72 (0.35 - 1.47)	
5	1.88 (0.66 - 5.77)		1.04 (0.52 - 2.07)	

[*] *P-value from likelihood ratio test..*
[±] *Analyses performed using continuous variables, quantile/group odds ratios presented for interpretation purposes. OR, odds ratio; CI, confidence interval; PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CVD, cardiovascular disease, TIA, transient ischaemic attack; CVA, cerebrovascular accident; PRS, polygenic risk score.*

Multivariable associations with cranial ischaemic complications in 2022 ACR/EULAR classification criteria fulfilling patients

The model optimized for cranial ischaemic complications in GCA using elastic net regression was repeated in just patients who fulfilled the 2022 ACR/EULAR classification criteria for GCA. There were a total of 51 patients who fulfilled the 1990 ACR classification criteria for GCA, but did not meet the 2022 classification criteria. Furthermore, 25 individuals did not meet the 1990 ACR criteria, but did fulfil

the 2022 criteria. An additional 207 cases who had an "unknown" score for the 1990 criteria and fulfiled the 2022 ACR criteria.

The results of this analysis were largely consistent with those from the primary analysis (**Supplementary Table 18**). Age at diagnosis (AOR[95% CI]=1.50 [0.67 to 3.50], P=3.69 x 10^{-3}, for the highest [≥80 years] versus lowest [<60 years] decade) and anticoagulant therapy (AOR[95% CI]=0.21 [0.05 to 0.66], P=7.76 x 10^{-3}) remained strongly associated with cranial ischaemic complications, with the same direction of effect. Interestingly, the platelet count PRS was also strongly associated with the outcome in this analysis (AOR[95% CI]=0.41 [0.22 to 0.73], P=0.04), suggesting that an increase in heritable platelet levels could be protective of cranial ischaemic complications in GCA.

ESR levels were strongly associated with cranial ischaemic complications in the cohort who had their diagnosis confirmed by imaging or temporal artery biopsy, in the negative direction (AOR[95% CI]=0.37 [0.17 to 0.8], P=0.02). This strength of association was not observed in the cohort fulfilling the 2022 ACR criteria.

Supplementary Table 18. Multivariable associations with cranial ischaemic complications in GCA at presentation, including: solely patients who fulfilled the 2022 ACR/EULAR classification criteria for GCA diagnosis.

Trait	Patients who fulfilled 1990 ACR criteria for GCA diagnosis		Patients who fulfilled 2022 ACR criteria for GCA diagnosis		Patients with confirmatory diagnostic imaging or temporal artery biopsy	
	OR (95%CIs)	*P*-value*	OR (95%CIs)	*P*-value*	OR (95%CIs)	*P*-value*
Age at diagnosis±		2.52 x 10^{-3}		3.69 x 10^{-3}		8.34 x 10^{-5}
< 60 years	1.00		1.00		1.00	
60 to < 70 years	0.58 (0.28 to 1.25)		0.54 (0.26 to 1.19)		1.31 (0.21 to 25.59)	
70 to < 80 years	1.06 (0.54 to 2.23)		1.00 (0.50 to 2.14)		2.81 (0.48 to 53.58)	
≥ 80 years	1.6 (0.73 to 3.66)		1.50 (0.67 to 3.50)		5.87 (0.93 to 115.65)	
PMR	0.8 (0.55 to 1.16)	0.26	0.79 (0.53 to 1.15)	0.27	0.87 (0.51 to 1.47)	0.95

ESR quintiles [mm/h] [±]		0.12		0.06		0.02
< 29	1.00		1.00		1.00	
29 to < 49	0.49 (0.27 to 0.9)		0.45 (0.24 - 0.84)		0.33 (0.14 to 0.75)	
49 to < 69	1.13 (0.66 to 1.95)		1.16 (0.66 - 2.06)		0.84 (0.39 to 1.80)	
69 to <96	0.62 (0.34 to 1.1)		0.66 (0.36 - 1.21)		0.38 (0.17 to 0.86)	
≥ 96	0.63 (0.36 to 1.11)		0.63 (0.35 - 1.14)		0.37 (0.17 to 0.80)	
CVD composite	1.13 (0.65 to 1.93)	0.72	1.14 (0.64 - 1.99)	0.68	0.91 (0.37 to 2.09)	0.92
TIA/CVA	1.34 (0.62 to 2.82)	0.50	1.41 (0.64 - 3.04)	0.45	2.47 (0.76 to 8.02)	0.33
Hyperlipidaemia	1.44 (0.9 to 2.26)	0.33	1.44 (0.90 - 2.29)	0.34	1.94 (0.99 to 3.79)	0.22
Hypertension	1.34 (0.93 to 1.95)	0.11	1.34 (0.92 - 1.96)	0.15	1.20 (0.72 to 2.00)	0.47
Antiplatelet therapy	1.25 (0.73 to 2.1)	0.43	1.29 (0.74 - 2.20)	0.42	0.85 (0.35 to 1.91)	0.69
Anticoagulant therapy	0.21 (0.05 to 0.62)	4.95×10^{-3}	0.21 (0.05 - 0.66)	7.76×10^{-3}	0.10 (0.01 to 0.62)	0.02
Cholesterol-lowering therapy	0.68 (0.41 to 1.12)	0.24	0.64 (0.38 - 1.06)	0.18	0.57 (0.28 to 1.15)	0.20
Platelet count PRS quintiles[±]		0.11		0.04		0.10
1	1.00		1.00		1.00	
2	0.55 (0.31 to 0.94)		0.53 (0.30 - 0.92)		0.42 (0.19 to 0.91)	
3	1.03 (0.6 to 1.75)		0.89 (0.52 - 1.54)		0.97 (0.46 to 2.04)	
4	0.69 (0.41 to 1.17)		0.60 (0.35 - 1.02)		0.47 (0.22 to 0.97)	
5	0.45 (0.25 to 0.81)		0.41 (0.22 - 0.73)		0.42 (0.18 to 0.93)	
TIA PRS quintiles[±]		0.13		0.17		0.12
1	1.00		1.00		1.00	
2	0.99 (0.55 to 1.76)		0.94 (0.52 - 1.70)		1.27 (0.57 to 2.86)	
3	1.21 (0.67 to 2.19)		1.25 (0.69 - 2.29)		1.24 (0.55 to 2.81)	
4	1.05 (0.59 to 1.87)		1.00 (0.55 - 1.81)		0.94 (0.41 to 2.11)	
5	1.29 (0.74 to 2.26)		1.18 (0.67 - 2.09)		1.47 (0.70 to 3.18)	

[*] *P-value from likelihood ratio test..*

[±] *Analyses performed using continuous variables, quantile/group odds ratios presented for interpretation purposes.*

OR, odds ratio; CI, confidence interval; PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CVD, cardiovascular disease, TIA, transient ischaemic attack; CVA, cerebrovascular accident; PRS, polygenic risk score.

Multivariable associations with secondary outcomes in GCA

The model optimized for cranial ischaemic complications in GCA using elastic net regression was tested on a secondary outcome of transient cranial ischaemic manifestations in GCA. In these multivariable analyses, no variables were associated with transient cranial ischaemic manifestations at a likelihood ratio [LR] test *P-value* < 0.05 (**Supplementary Table 19**).

Supplementary Table 19. Associations with transient cranial ischaemic features or extra-cranial manifestations in GCA at presentation, adjusted for sociodemographic, clinical and genetic factors.

Trait	Transient cranial ischaemic features		Extra-cranial manifestations	
	OR (95%CIs)	*P*-value*	OR (95%CIs)	*P*-value*
Age at diagnosis±		0.06		0.09
< 60 years	1.00		1.00	
60 to < 70 years	0.95 (0.49 to 1.85)		0.85 (0.35 to 2.31)	
70 to < 80 years	1.28 (0.67 to 2.47)		0.78 (0.32 to 2.10)	
≥ 80 years	1.65 (0.75 to 3.64)		0.42 (0.11 to 1.49)	
PMR	1.45 (1.04 to 2.04)	0.05	1.99 (1.21 to 3.29)	0.01
ESR Quintiles ±		0.30		0.99
< 29	1.00		1.00	
29 to < 49	0.88 (0.52 to 1.51)		1.22 (0.56 to 2.69)	
49 to < 69	1.48 (0.88 to 2.51)		0.9 (0.39 to 2.04)	
69 to <96	1.10 (0.65 to 1.87)		0.72 (0.31 to 1.68)	
≥ 96	1.56 (0.93 to 2.64)		1.08 (0.50 to 2.36)	
CVD composite	0.79 (0.47 to 1.32)	0.38	2.39 (1.17 to 4.75)	0.02
TIA/CVA	1.94 (0.91 to 4.26)	0.1	0.55 (0.16 to 1.60)	0.33
Hyperlipidaemia	1.37 (0.89 to 2.14)	0.34	1.29 (0.67 to 2.42)	0.39
Hypertension	1.16 (0.82 to 1.64)	0.55	1.14 (0.67 to 1.92)	0.54
Antiplatelet therapy	1.09 (0.66 to 1.81)	0.8	0.75 (0.33 to 1.60)	0.57
Anticoagulant therapy	0.45 (0.21 to 0.96)	0.08	0.41 (0.09 to 1.34)	0.18
Cholesterol-lowering therapy	1.00 (0.62 to 1.61)	0.89	0.9 (0.44 to 1.81)	0.65
Platelet count PRS quintiles±		0.92		0.97
1	1.00		1.00	
2	1.27 (0.76 to 2.12)		1.42 (0.64 to 3.22)	
3	1.31 (0.76 to 2.29)		0.83 (0.32 to 2.06)	
4	1.41 (0.84 to 2.36)		1.47 (0.68 to 3.30)	
5	0.98 (0.58 to 1.64)		1.33 (0.61 to 2.98)	
TIA PRS quintiles±		0.3		0.81
1	1.00		1.00	
2	0.88 (0.52 to 1.51)		0.76 (0.36 to 1.63)	
3	1.48 (0.88 to 2.51)		0.93 (0.43 to 2.01)	

4	1.10 (0.65 to 1.87)	0.77 (0.34 to 1.69)
5	1.56 (0.93 to 2.64)	0.60 (0.27 to 1.31)

[*] *P-value from likelihood ratio test.*
[±] *Analyses performed using continuous variables, quantile/group odds ratios presented for interpretation purposes.*

OR, odds ratio; CI, confidence interval; PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CVD, cardiovascular disease, TIA, transient ischaemic attack; CVA, cerebrovascular accident; PRS, polygenic risk score.

The cranial ischaemic complications in the GCA model were then tested for association with the secondary outcome of non-cranial ischaemic features in GCA. Of the variables in the model, two were associated with non-cranial ischaemic features in GCA (LR *P-value* < 0.05) (**Supplementary Table 19**): PMR symptoms at GCA diagnosis (AOR[95% CI]=1.99 [1.21 to 3.29], *P*=0.01), and a CVD composite (AOR[95% CI]=2.39 [1.17 to 4.75], *P* =0.02).

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