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Original article

Ischaemic manifestations in giant cell arteritis are associated with area level socio-economic deprivation, but not cardiovascular risk factors

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Abstract

Objectives. To determine whether ischaemic manifestations of GCA are associated with pre-existing hypertension, atherosclerosis or area-level socio-economic deprivation.

Methods. We conducted an observational study of rheumatologist/ophthalmologist-diagnosed GCA in eight UK centres. The main outcome measure was ischaemic manifestations observed during active GCA: visual loss/blurring, aura, diplopia, jaw/tongue/limb claudication, cerebral/myocardial ischaemia or scalp necrosis.

Results. Out of 271 patients, 222 had ischaemic manifestations. Adjusted odds ratios (ORs) for the influence of hypertension and atherosclerosis were 1.6 (95% CI 0.8, 3.1) and 1.5 (0.6, 3.5). The most striking finding was an association of ischaemic manifestations with increasing Index of Deprivation 2007 score: OR 4.2 (95% CI 1.3, 13.6) for the most-deprived quartile compared with the least-deprived quartile. Similar effect sizes were seen within each recruitment centre. Deprivation was associated with smoking and negatively associated with previous polymyalgia. However, neither of these variables, nor hypertension or atherosclerosis, appeared responsible for mediating the effect of deprivation on ischaemic complications. Smoking was not associated with ischaemic manifestations. Median symptom duration before treatment was 30 days; after adjusting for symptom duration, the OR for ischaemic complications was 3.2 (95% CI 1.0, 10.8) for the most-deprived quartile compared with the least-deprived quartile.

Conclusions. In GCA, area-level socio-economic deprivation was associated with ischaemic manifestations: this was not mediated by traditional cardiovascular risk factors. These findings are novel and require replication. Delay between first symptoms and treatment may play a role. Public awareness campaigns about GCA should aim especially to engage individuals living in more deprived areas to encourage early presentation and prompt treatment.

Key words: Giant cell arteritis, Social deprivation, Ischaemic manifestations, Atherosclerosis, Smoking.

CLINICAL SCIENCE

Introduction

GCA (or temporal arteritis) is a medical emergency requiring immediate steroid treatment to prevent permanent blindness or stroke. The UK incidence of GCA is 22/100 000/year [1]. Classical features include headache, scalp tenderness, abnormality of the temporal artery and

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†See Appendix 1 for a list of the members of the UK GCA Consortium, available as supplementary data at *Rheumatology* Online.

high inflammatory markers in persons >50 years of age. GCA may occur before, together with or following PMR, a steroid-responsive inflammatory musculoskeletal condition [2, 3]. Steroid treatment may be required for years, and frequently produces adverse effects [4]. Recent British Society for Rheumatology guidelines stress the need for immediate treatment with systemic steroids in suspected cases to reduce the risk of permanent visual loss. Patients with ischaemic manifestations at presentation, including transient visual loss or jaw/tongue claudication, are at higher risk of future blindness [5] and require treatment with higher doses of oral or parenteral steroid [6]. Ischaemic manifestations are, therefore, a key warning sign of severe disease in GCA; it would be useful to be able to identify patients at risk before potentially irreversible end-organ ischaemic manifestations occur, as well as improving our understanding of why some patients with GCA develop complications.

Pre-existing atherosclerosis [7] and hypertension [7, 8] have been identified as potential risk factors for ischaemic manifestations in GCA. Smoking may be a GCA susceptibility risk factor [9–11]. Our main aim in this study was to investigate whether pre-existing vascular disease predicted ischaemic manifestations in GCA in this cohort: this may be relevant to particular aspects of GCA pathogenesis.

Biological ageing, the major risk factor for GCA, is itself associated with endothelial dysfunction and low-grade systemic inflammation (inflamm–ageing) [12]; both age-related endothelial dysfunction [13, 14] and low-grade systemic inflammation [15, 16] are exacerbated in the presence of atherosclerosis or its risk factors, including hypertension [17]. Hypertension was of particular interest to us given its close relationship with the renin–angiotensin axis [18, 19], which has powerful effects on many aspects of the entire vasculature [20].

Atherosclerosis and GCA also share many soluble and cellular effector mechanisms, including both local and circulating MCP-1 [21, 22], infiltrating T cells and activated macrophages [23]. Both diseases exhibit a common response to injury program, including neointimal proliferation [16, 23]. It therefore appeared plausible that factors associated with hypertension or atherosclerosis might also affect the severity of GCA, by modulating either the severity of the vasculitic lesion itself, or the ability of the end-organ vasculature to autoregulate tissue perfusion in the face of an upstream limitation of vascular flow.

UK primary care–based data suggest that GCA is more common in more affluent parts of the country [1]. Area-level socio-economic deprivation is a powerful predictor of carotid atherosclerosis in those >50 years of age, independent of classical cardiovascular risk factors such as smoking or hypertension [24]. Furthermore, adverse socio-economic factors are associated with higher levels of IL-6 and CRP in older adults, independent of the presence of atherosclerotic conditions [25, 26]. Socio-economic factors are also associated with altered immune function [27, 28]. Previous studies have not examined social deprivation as an independent predictor of ischaemic complications in GCA. The objective of this study was to determine whether ischaemic manifestations of GCA are associated with pre-existing hypertension, atherosclerosis or area-level socio-economic deprivation.

Methods

Study population and study protocol

Ethical approval was granted by the York Research Ethics Committee, reference 05/Q1108/28, and all participants provided informed consent. Cases of GCA were identified from departmental and/or histology records at each centre between 2005 and 2009. All cases either fulfilled ACR classification criteria for GCA (247/271), were biopsy proven (178/271), or had classical clinical features sufficient for a firm clinical diagnosis. All patients were treated with systemic steroids according to standard clinical practice. Data were obtained by patient interview combined with contemporaneously recorded clinical notes. Here, we report cases with full data on the outcome measure (ischaemic manifestations) and on all three predefined variables of interest (hypertension, atherosclerosis and deprivation). In multivariable analysis, cases without full data on all variables were coded as missing.

Variables studied

The three exposures, or variables of interest, assessed in this study were pre-existing hypertension (pharmacologically treated or blood pressure $\geqslant$140/90 mm Hg on two or more occasions), atherosclerosis (clinically overt myocardial, cerebral or limb ischaemia unrelated to GCA) and area-level socio-economic deprivation [Index of Multiple Deprivation 2007 (IMD2007), a higher value indicating greater deprivation]. The IMD2007 is the UK government's preferred measure of socio-economic deprivation for England, based on seven distinct domains of deprivation: income, employment, health, education, barriers to housing and services, crime and living environment. The IMD2007 statistic is a weighted, area-level aggregation of these specific dimensions of deprivation. The IMD2007 has been calculated for each lower layer super output area (LSOA) in England. Each LSOA contains an average of 1500 individuals. Postcodes were converted to IMD2007 scores using the GeoConvert tool http://geoconvert.mimas.ac.uk/index.htm via www.census.ac.uk. To confirm the validity of the IMD2007 result, data about the levels of family income and education were also generated from postcodes using the A Classification of Residential Neighbourhoods (ACORN) index, which uses a combination of census and survey data: http://www.caci.co.uk/acorn-classification.aspx. Other relevant variables (shown in Table 1) were recorded where data were available; the duration of GCA symptoms before first treatment with steroids and the starting dose of steroids used to treat the GCA symptoms were also recorded. Smoking status was recorded as never, ex or current, with pack-years, smoking intensity (cigarettes/day) and number of years since stopping smoking all

Table 1 Predictors of ischaemic manifestations

Predictor	Proportion with ischaemic manifestations (%)	Unadjusted OR (95% CI)	Overall *P*-value for variable (Wald)
Variables of interest			
Hypertension[a]			
No	126/159 (79.2)	1.00 (reference)	0.175
Yes	96/112 (85.7)	1.57 (0.82, 3.02)	
Atherosclerosis[a]			
No	175/217 (80.6)	1.00 (reference)	0.278
Yes	47/54 (87.0)	1.61 (0.68, 3.82)	
Deprivation			
Least deprived	46/59 (78.0)	1.00 (reference)	0.036
Second quartile	50/68 (73.5)	0.79 (0.35, 1.78)	
Third quartile	68/82 (82.9)	1.37 (0.59, 3.19)	
Most deprived	58/62 (93.5)	4.10 (1.25, 13.41)	
Status prior to onset of GCA			
Gender			
Male	56/78 (71.8)	1.00 (reference)	0.005
Female	165/191 (86.4)	2.49 (1.31, 4.75)	
On steroids for PMR[a]			
No	184/223 (82.5)	1.00 (reference)	0.324
Yes	28/37 (75.7)	0.66 (0.29, 1.51)	
Prior treatment for PMR[a]			
No	172/205 (83.9)	1.00 (reference)	0.099
Yes	40/54 (74.1)	0.55 (0.27, 1.12)	
Ischaemic heart disease[a]			
No	185/230 (80.4)	1.00 (reference)	0.142
Yes	37/41 (90.2)	2.25 (0.76, 6.64)	
Cerebrovascular disease[a]			
No	208/255 (81.6)	1.00 (reference)	0.553
Yes	14/16 (87.5)	1.58 (0.35, 7.20)	
Peripheral vascular disease[a]			
No	213/261 (81.6)	1.00 (reference)	0.507
Yes	9/10 (90.0)	2.03 (0.25, 16.4)	
Smoker at onset of GCA			
Never	85/105 (81.0)	1.00 (reference)	0.818
Ex	86/103 (83.5)	1.19 (0.58, 2.43)	
Current	44/52 (84.6)	1.29 (0.53, 3.17)	
Aspirin[a]			
No	166/210 (79.0)	1.00 (reference)	0.038
Yes	53/58 (91.4)	2.81 (1.06, 7.45)	
Statin[a]			
No	184/223 (82.5)	1.00 (reference)	0.455
Yes	35/45 (77.8)	0.74 (0.34, 1.62)	
High cholesterol[a]			
No	155/188 (82.4)	1.00 (reference)	0.476
Yes	47/60 (78.3)	0.77 (0.37, 1.58)	
Diabetes[a]			
No	201/245 (82.0)	1.00 (reference)	0.869
Yes	8/10 (80.0)	0.88 (0.18, 4.27)	
Family history of atherosclerosis			
No	104/133 (78.2)	1.00 (reference)	0.219
Yes	49/57 (86.0)	1.71 (0.73, 4.01)	
Features of GCA			
Biopsy, if done			
Negative	37/44 (84.1)	1.00 (reference)	0.520
Positive	145/178 (81.5)	0.80 (0.40, 1.58)	
Tender temporal artery			
No	76/95 (80.0)	1.00 (reference)	
Yes	113/138 (81.9)	1.13 (0.58, 2.19)	
Started on <30 mg prednisolone			
No	184/227 (81.1)	1.00 (reference)	0.718
Yes	13/14 (92.9)	3.04 (0.39, 23.85)	0.291

The proportion with ischemic manifestations is shown as *n*/*N*, where *N* is the number with the attribute shown in the first column and *n* is the number of those *N* cases with ischaemic manifestations. [a]Before diagnosis of GCA. For example, in the first row, 112 out of 271 cases had pre-existing hypertension, and 96 (85.7%) of these 112 had ischaemic manifestations, whereas 126 (79.2%) of the remaining 159 had ischaemic manifestations, which was not a significantly different proportion ($P = 0.175$). OR and *P*-value are calculated by logistic regression. For simplicity, this table shows categorical predictor variables only; statistics for continuous variables are given in the main text.

Table 2 Ischaemic manifestations within the study

Ischaemic manifestations of GCA	Type of complication	*n* (%) of 271 cases
Ischaemic manifestations (all)		222 (81.9)
Visual/neurological ischaemic manifestations		151 (55.7)
Irreversible visual/neurological complications	Irreversible visual loss	46 (17.0)
	Irreversible diplopia	5 (1.8)
	Stroke	3 (1.1)
Other irreversible complications	Arterial stenosis to limb	6 (2.2)
	Mycocardial infarction	1 (0.4)
Transient ischaemic manifestations	Transient visual loss	100 (36.9)
	Transient diplopia	33 (12.2)
	Visual aura or hallucinations	26 (9.6)
	Transient cerebral ischaemia	7 (2.6)
	Jaw claudication	147 (54.2)
	Tongue claudication	20 (7.4)
	Limb claudication	20 (7.4)
	Angina	4 (1.5)

By definition, all these ischaemic manifestations were judged to be caused by active GCA rather than being coincidental or caused by steroid therapy. The percentages in the right-hand column add up to >100% because many patients suffered more than one ischaemic manifestation.

recorded. The temporal artery biopsy (if performed) was classed as positive or negative using the original histopathology report.

Outcome measures

The pre-specified outcome measure was ischaemic manifestations (Table 2), defined as visual loss or blurring, visual aura, diplopia, jaw/tongue/limb claudication, cerebral or myocardial ischaemia or scalp/tongue necrosis observed during a period of active GCA.

Statistical analysis

In a previous study pre-existing ischaemic heart disease increased the risk of severe ischaemic manifestations in GCA [unadjusted odds ratio (OR) = 5.3; 95% CI 1.6, 16.8], with the unadjusted OR for hypertension also exceeding 5.0 [7]. Based on these data, power calculations suggested that 174 GCA cases would be required to detect an OR of 5.0 for atherosclerosis, with power 80% and two-tailed $P < 0.05$.

Multivariable logistic regression [29, 30] was used to model the association of ischaemic manifestations with each of the three variables of interest. For each variable of interest, potential confounders were chosen before performing univariable analysis based on prior literature review and clinical reasoning. Based on a 10 events per predictor 'rule of thumb', up to a total of four predictors could be included in the model; the univariable analysis was therefore used to select those confounders with $P < 0.25$ [30]. The adjusted OR for the variable of interest was taken as the gold-standard OR. To improve model precision without sacrificing accuracy, confounders were sequentially removed from the model unless removal produced a >10% change in the estimated OR [29]. Confounders chosen for hypertension were age, gender and deprivation. Confounders chosen for atherosclerosis were hypertension, gender, deprivation and family history of atherosclerosis. Smoking was not included because of a lack of effect in univariable analysis. Confounders chosen for deprivation were age and gender. Aspirin therapy was not selected as a confounder because of the complexity of the casual relationships with the other variables. For each of the three variables of interest, a Mantel–Haentsel test was performed to stratify the association by recruitment centre.

In an exploratory analysis, potential mediators were also included in the models [31], although formal significance testing was not performed due to power limitations. A secondary analysis was also performed to determine whether each of the three variables of interest predicted irreversible ischaemic complications. Age was controlled for in the multivariable analyses using this secondary outcome measure due to the significant univariable association with this secondary outcome measure. Standard logistic regression diagnostics (Pearson residual, leverage and deviance residuals) and influential case analyses were performed. Analyses were performed in Stata SE version 10 (College Station, TX, USA) (for Mantel–Haentsel tests and logistic regression diagnostics) and SPSS version 15 (Chicago, IL, USA) (all other analyses). Two-tailed $P < 0.05$ was taken as indicating statistical significance for all analyses.

Results

Of the 271 patients, 222 (81.9%) had ischaemic manifestations, the details of which are shown in Table 2.

Univariable analyses

Ischaemic manifestations were associated with deprivation and gender, but not with any other categorical variable except aspirin therapy (Table 1). There was no

association with continuous variables (median, interquartile range) including age at diagnosis (72, 67–78 years), plasma viscosity (PV) (1.96, 1.82–2.10 mPa s), ESR (70, 44.5–91 mm/h), CRP (60, 29.9–118 mg/l) or symptom duration, defined as the time between first onset of GCA symptoms and first steroid treatment (30, 12.25–78.5 days); symptom duration data were available in 248 (92%) out of 271 patients. Ischaemic manifestations were also not associated with any smoking variable, including never/ex/current smoking, pack-years, smoking intensity (cigarettes/day) or time in years since stopping smoking. Irreversible ischaemic complications were associated with older age at diagnosis ($P = 0.015$), but not with any other continuous or categorical variable measured. We found no evidence that ischaemic manifestations or complications were associated with a lower initial treatment dose of prednisolone. Patients who had been treated for PMR in the past had their GCA symptoms identified more rapidly: the median symptom duration was 16 days in these patients, compared with 34 days in the rest ($P = 0.005$). There was no evidence for an association of ischaemic features with either the time taken to reach a stable dose of 5 mg prednisolone ($n = 146$ with available data, $P = 0.458$) or the time taken to stop steroids entirely ($n = 104$ with available data, $P = 0.394$).

The cases were divided into four groups based on quartiles of IMD2007 score (the groups were not exactly equal in size because some cases with different postcodes shared the same IMD2007 score). Age and gender were similar across all four quartiles of IMD2007. Median (interquartile range) IMD2007 score for the whole group was 13.4 (8.5–23.0): in those with ischaemic manifestations the median (interquartile range) IMD2007 was 14.0 (8.6–25.0), whereas in those without ischaemic manifestations it was 10.9 (7.6–16.1). For comparison, median (interquartile range) IMD2007 for all LSOAs in England is 17.1 (9.6–30.2).

Based on the ACORN postcode classifications, the presence of ischaemic features was also significantly associated with a higher percentage of individuals with no formal educational qualifications ($P = 0.043$), a lower percentage of individuals educated to degree level or equivalent ($P = 0.047$) and a lower family income ($P = 0.011$) as well as a higher IMD2007 deprivation score ($P = 0.007$).

Multivariable modelling

Ischaemic manifestations were not significantly associated with hypertension [unadjusted OR = 1.6 (95% CI 0.8, 3.0), OR adjusted for deprivation = 1.6 (95% CI 0.8, 3.1)] or atherosclerosis [unadjusted OR = 1.6 (95% CI 0.7, 3.8), OR adjusted for hypertension = 1.5 (95% CI 0.6, 3.5)]. An association of ischaemic manifestations was identified with social deprivation that was not confounded by age or gender: OR = 4.2 (95% CI 1.3, 13.6) for the most-deprived quartile compared with the least-deprived quartile (Table 3).

Irreversible ischaemic complications were not significantly associated with either hypertension or atherosclerosis. Controlling for the age at onset of GCA, the OR for irreversible ischaemic complications was 3.0 (95% CI 1.1, 7.9; $P = 0.029$) for the most-deprived quartile compared with the least-deprived quartile. Age made a significant independent contribution to this model; the OR for each 10-year increase in age was 1.5 (95% CI 1.0, 2.3; $P = 0.042$). There was no confounding by gender.

Table 3 Multivariable analysis for the influence of social deprivation on ischaemic manifestations

Models run to determine presence of confounding ($n = 267$ for all)	Estimated OR for deprivation, above median compared with below median (95% CI)
Deprivation, age, gender	2.103 (1.092, 4.048)
Deprivation, age	2.092 (0.959,1.040)
Deprivation, gender	2.100 (1.094, 0.760)
Deprivation	2.096 (1.103, 3.985)

Stratification by recruitment centre

To investigate whether between-centre effects were responsible for the association of deprivation with ischaemic manifestations, a simplified analysis was performed, stratified by centre. The effect size was similar within each recruitment centre (Table 4) and there was no evidence for heterogeneity of ORs between recruitment centres ($P = 0.947$). In equivalent analyses, no evidence of between-centre effects was seen for atherosclerosis or hypertension.

Potential mediators of deprivation

A higher deprivation score was associated with greater tobacco exposure in pack-years (Spearman's $\rho = 0.217$, $P = 0.001$, $n = 239$) and with a lower probability of having a prior history of treated PMR at presentation with GCA ($P = 0.004$, $n = 259$), not including those whose GCA presented with PMR-like symptoms within the same episode of illness. However, tobacco exposure was not associated with ischaemic manifestations. Deprivation was not significantly associated with atherosclerosis ($P = 0.127$, $n = 271$), with hypertension ($P = 0.895$, $n = 271$), with the duration of symptoms before first steroid treatment (Spearman's $\rho = 0.086$, $P = 0.177$, $n = 248$) or with the dose of steroids given for GCA (Spearman's $\rho = 0.018$, $P = 0.782$, $n = 241$). On multivariable logistic regression modelling, the only potential mediator that substantively reduced the OR for deprivation was the duration of symptoms (Table 5). Fourteen cases with atypical presentations were treated initially with <30 mg prednisolone (as for pure polymyalgia); none of these 14 cases had irreversible ischaemic complications, and the effect of deprivation on ischaemic manifestations remained significant when these 14 cases with atypical presentations were omitted from analysis (Table 5, last row). Repeating the analysis restricted to the never-smoker cases, the magnitude of the effect of social deprivation was not substantively

TABLE 4 Stratification by recruitment centre (Mantel–Haentzel analysis)

Area	Recruitment centre	*n*	IMD score, median (quartiles)	OR (95% CI) for one-unit increase in deprivation quartile	*P*-value
West Yorkshire	East Leeds	26	13.85 (11.16–25.67)	1.627 (0.690, 3.839)	0.266
	Wharfedale	60	11.93 (6.93–18.01)	1.395 (0.701, 2.775)	0.343
	West Leeds	73	19.95 (11.69–37.31)	1.753 (1.061, 2.894)	0.028
Mid Yorkshire	Pinderfields, Pontefract	18	21.62 (13.44–39.49)	5.048 (1.043, 24.443)	0.044
	Dewsbury	16	16.84 (9.99–27.00)	1.934 (0.308, 12.146)	0.482
North Yorkshire	York	17	9.85 (6.02–12.64)	1.588 (0.419, 6.023)	0.496
	Harrogate	34	8.21 (5.19–12.37)	1.538 (0.470, 5.032)	0.477
Essex	Southend	27	11.79 (8.03–20.24)	1.733 (0.583, 5.156)	0.323

TABLE 5 Potential mediators of deprivation

Predictors in multivariable model	Adjusted OR (95% CI) of deprivation for ischaemic features compared with least-deprived quartile			Overall *P*-value for deprivation variable
	Second quartile	Third quartile	Most-deprived quartile	
Deprivation				
Unadjusted	0.785 (0.346, 1.779)	1.373 (0.591, 3.188)	4.098 (1.252, 13.411)	0.036
Hypertension	0.781 (0.343, 1.776)	1.330 (0.570, 3.103)	4.134 (1.260, 13.565)	0.037
Atherosclerosis	0.795 (0.350, 1.805)	1.364 (0.587, 3.172)	4.011 (1.223, 13.149)	0.043
Smoking	0.743 (0.318, 1.736)	1.437 (0.580, 3.559)	3.951 (1.154, 13.519)	0.041
Prior diagnosis of PMR	0.690 (0.297, 1.606)	1.270 (0.534, 3.020)	4.968 (1.305, 18.907)	0.024
On aspirin before GCA	0.808 (0.352, 1.855)	1.357 (0.578, 3.186)	4.498 (1.361, 14.863)	0.030
Symptom duration	0.697 (0.294, 1.654)	1.133 (0.464, 2.771)	3.211 (0.953, 10.821)	0.080
Steroid <30 mg at onset of GCA	0.820 (0.340, 1.979)	1.214 (0.493, 2.994)	3.811 (1.127, 12.833)	0.076
Omitting 14 cases started on <30 mg prednisolone	0.744 (0.322, 1.721)	1.256 (0.530, 2.977)	3.837 (1.156, 12.738)	0.044

Each row in the table refers to the OR of deprivation with regard to ischaemic features. The top data row shows the unadjusted OR of deprivation. The next seven data rows refer to the OR of deprivation, adjusted for each candidate mediator in turn in a series of seven different models (adjusting for hypertension, atherosclerosis, smoking, prior diagnosis of PMR, on aspirin before GCA, symptom duration, or steroid <30 mg at onset of GCA). The last data row is an unadjusted OR for deprivation, omitting 14 cases started on <30 mg prednisolone. Symptom duration, treated as a continuous variable, was log-transformed. Smoking was classified as a categorical variable (never, ex- or current smoker).

changed (OR = 4.8; 95% CI 0.5, 42.9 for the most-deprived quartile compared with the least-deprived quartile), although statistical significance was lost due to the smaller numbers. Similarly, on repeating the analysis excluding those previously treated for PMR, the magnitude of the effect of social deprivation increased (OR = 5.3; 95% CI 1.3, 21.1 for the most-deprived quartile compared with the least-deprived quartile), although the social deprivation variable lost its overall statistical significance due to the smaller numbers. Thus we found no evidence that deprivation exerted its influence on ischaemic manifestations via smoking, prior diagnosis of PMR, or via any other measured variable, except possibly a partial influence via increasing the time between first symptoms and steroid treatment.

Finally, we sought to determine whether GCA was over-diagnosed (i.e. diagnosed in patients who did not really have the disease) in more affluent areas by comparing the rate of biopsy positivity in the four quartiles of deprivation (Table 6). No evidence was found for over-diagnosis of GCA (i.e. no excess of biopsy-negative or non-biopsied cases) in less-deprived areas.

Discussion

Our most striking finding was the novel association of area-level socio-economic deprivation with ischaemic manifestations of GCA. Despite adequate power, our study failed to detect any significant association of hypertension or atherosclerosis with ischaemic manifestations

Table 6 Comparison of rate of biopsy results in each quartile of social deprivation

Quartile of social deprivation	Biopsy		
	Positive, *n* (%)	Negative, *n* (%)	Biopsy not performed, *n* (%)
Least deprived	39 (66)	8 (14)	12 (20)
Second quartile	44 (67)	11 (17)	11 (17)
Third quartile	50 (61)	15 (18)	17 (21)
Most deprived	45 (73)	10 (16)	7 (11)

of GCA, as had been previously reported in a smaller study from Italy [7], despite being adequately powered to do so. The effect sizes we estimated were more consistent with those in a report from Spain [8]. In an exploratory analysis (Table 5), there was a suggestion that the effect of social deprivation on ischaemic manifestations may be partially mediated by increasing the time between first symptoms and first steroid dose. Our findings now require replication in an independent data set.

Strengths of this study include its size compared with previous studies [7, 8]. The multicentre design increases generalizability; there was no evidence for bias arising from between-centre differences. In one of the previous studies [8], atherosclerosis was assessed by enumerating classical cardiovascular risk factors, but this method assumes that each cardiovascular risk factor makes an equal and independent contribution to overall atherosclerosis burden. Instead, we defined hypertension and atherosclerosis each as binary variables, theoretically sacrificing some power for clinical validity. We also had a clear, prespecified modelling strategy based on standard approaches [29, 30] and we distinguished between confounders and mediators in assessing possible effects of deprivation on ischaemic features [31, 32].

We did not exclude biopsy-negative or non-biopsied cases if the clinical diagnosis was clear-cut, as in some centres at the time it was felt that a prompt biopsy was unnecessary in clinically classical cases, since the result would not alter management; clinical practice is now changing [6]. Retrospective case finding was a limitation, as some data were not collected contemporaneously. We chose to assess deprivation based on LSOAs, each comprising an average of 1500 individuals. Other proxies for individual-level socio-economic deprivation are less relevant for retired individuals; educational opportunities, for example, varied by decade of the 20th century, particularly for women. In future, larger studies perhaps these other factors could be included in the model.

Unexpectedly, the effect of deprivation on ischaemic features was much stronger than that of the binary variable atherosclerosis. It is possible that the relatively crude methods (patient history and notes review) used to assess hypertension/atherosclerosis were not sensitive enough to detect a real underlying association. Deprivation might be an even better proxy for atherosclerotic burden than the clinical atherosclerotic events recorded [24]; deprivation might also be a better proxy for atherosclerotic risk factors, such as tobacco exposure (deprivation was correlated with tobacco exposure in our data set). One potential explanation might be that individuals from more deprived backgrounds are less likely to be treated for atherosclerosis with low-dose aspirin, which has been suggested to protect against ischaemic manifestations in GCA [33]; however, contrary to this prediction, in our data set those already taking aspirin at GCA presentation had a higher incidence of ischaemic manifestations (Table 1), suggesting that in this data set aspirin therapy might be a proxy for risk of atherosclerosis. However, when predefining our variables of interest we considered aspirin therapy too likely to be affected by other variables, making the results difficult to interpret. Deprivation is also associated with other possible risk factors for atherosclerosis, which we did not measure in this study, including diet, sunlight exposure (influencing vitamin D levels), overcrowding and psychosocial stress. All of these factors may modulate not only autoimmune responses, but also susceptibility to infection. Infections have been suspected to play a role in vasculitis [34]; the incidence of GCA in one report was found to be clustered within populations, possibly coinciding with infectious outbreaks [35]. Our data appear to contradict a report from primary care that GCA is more common in affluent areas of the UK [1], but in that study the GCA diagnosis was only validated from clinical notes in a sample of the data set. We found no evidence that GCA is over-diagnosed in less-deprived areas, but could not exclude the possibility that under-diagnosis of GCA without ischaemic manifestations might be more likely in deprived areas, where, for a variety of reasons, individuals may have less ready access to medical care. Social deprivation may delay presentation of GCA to medical care until ischaemic manifestations supervene. The effect of deprivation on ischaemic features lost significance after controlling for the time between first symptoms and first steroid dose, with a reduction in the estimated effect size; this suggests that deprivation may influence ischaemic manifestations at least partly by delaying effective treatment of GCA. Early, atypical presentation with polymyalgic symptoms, on the other hand, did not appear to explain the effect of deprivation on ischaemic features.

The time between first symptoms and first steroid dose has been proposed as a key performance measure in future audits of GCA treatment [6]; our data suggest

improving symptom to steroid time may be relatively more challenging in deprived areas. The current study underlines the delayed recognition of this ischaemic disease with a median time between first symptoms and first steroid dose of 30 days, similar to that in other recent reports [36, 37]. Studies of delays in presentation of other diseases have suggested that prior knowledge or awareness about the disease is a key factor in triggering consultation regarding a person's symptoms [38, 39]. Few of the patients interviewed as part of our study had ever heard of GCA before their diagnosis, unless they had previously been treated for PMR and warned about potential symptoms of GCA; it is interesting that these patients had a significantly shorter symptom to steroid time than those who did not receive a prior diagnosis of PMR. The success of the UK ACT F.A.S.T campaign (http://www.nhs.uk/actfast/Pages/stroke.aspx) in increasing earlier presentation and successful thrombolysis of hyperacute stroke shows the benefit of awareness-raising campaigns in reducing irreversible ischaemic manifestations in patients with an ischaemic prodrome. Our findings underline the need for an awareness-raising campaign to reach everyone who might be affected by GCA, regardless of socio-economic status. Given that those with ischaemic manifestations at presentation require higher doses of steroids, prompt presentation to medical care and prompt diagnosis may be important in reducing the burden not only of potentially irreversible ischaemic manifestations, but also of steroid toxicity in this patient group.

Rheumatology key message

- In this study, area-level socio-economic deprivation was associated with ischaemic manifestations of GCA.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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