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Are Ethnicity, Social Grade, and Social Deprivation Associated With Severity of Thyroid-Associated Ophthalmopathy?

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Purpose: Previous studies have extensively investigated the pathophysiology, genetics, and lifestyle risk factors of thyroid-associated ophthalmopathy (TAO). The aim of this study was to investigate the independent contribution of ethnic origin, social grade, and level of social deprivation to TAO severity in a large, multiethnic, and urban population.

Methods: Retrospective case note review of all TAO patients seen at Birmingham and Midland Eye Centre, United Kingdom over a 14-year period. Ethnicity (White, Asian, or Black) was recorded, and residence postcode was used to determine social grade (National Readership Survey classification) and level of social deprivation (Index of Multiple Deprivation 2007). TAO severity was defined by European Group on Graves' Orbitopathy criteria. Moderate-to-severe: necessity for TAO treatment with oral or intravenous steroid, long-term immunosuppressants, or orbital radiotherapy. Sight-threatening: presence of dysthyroid optic neuropathy (DON) or need for urgent orbital decompression surgery. Multivariable logistic regression was performed to measure the independent influence of ethnicity, social grade, and social deprivation on indicators of severe TAO.

Results: Lower social grade was significantly associated with increased odds ratio (OR) of TAO patients having severe TAO, including treatment with oral (OR: 2.3 (95% CI 1.1–5.1) $p = 0.03$) and intravenous steroid (OR: 2.6 (95% CI 1.0–7.0) $p = 0.04$) and DON (OR: 4.0 (95% CI 1.2–12.7) $p = 0.02$), compared with those of highest social grade. Similar results were observed for social deprivation. Ethnicity had no independent association with any measure of TAO severity.

Conclusions: In this cohort, lower social grade and higher social deprivation, but not ethnicity, had independent, statistically significant association with more severe TAO.

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Thyroid-associated ophthalmopathy (TAO), also known as thyroid eye disease or Graves' Orbitopathy, is an inflammatory orbital condition of multifactorial aetiology which, although often mild and self-limiting, may be sight-threatening in 3% to 5%.[1,2]

The European Group on Graves' Orbitopathy (EUGOGO) recommends classification of TAO severity in 3 categories (Table 1). Numerous studies have extensively investigated the pathogenesis, genetic susceptibility, lifestyle risk factors, and psychosocial effects of TAO. However, as yet, there appears to have been little consideration of ethnicity, socioeconomic position, or level of social deprivation as influences on the presentation, activity or severity of TAO, nor on the eventual quantifiable burden of medical and surgical intervention.

Ethnicity and social grade have previously been shown to be determinants of disease prevalence and severity in a range of inflammatory and noninflammatory systemic conditions (e.g., hypertension, cardiovascular and renal disease, diabetes mellitus, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis)[3–8] and also ophthalmic conditions (e.g., primary open angle and primary angle closure glaucoma, keratoconus, cataract, retinopathy of prematurity, refractive errors),[9–13] but such literature in TAO is limited.

Tellez at al.[14] (1992) were the first to consider the influence of ethnicity on TAO, comparing ophthalmic signs in European and Asian (predominantly from the Indian subcontinent) patients with newly diagnosed Graves' disease (GD) presenting to an endocrinology clinic. This study found that the prevalence of TAO and overall risk of TAO development in Europeans were 6.4 times higher than that of Asian patients. However, Lim et al.[15] (2008) found similar prevalence of TAO in Asian (Malay, Chinese, and Indian) patients with GD as compared with Caucasian GD patients.

It has been proposed that anatomical variations (e.g., orbital dimensions such as depth and apex width, eyelid configuration, and normal upper limit of proptosis measurements) and differences in the frequency of genetic polymorphisms (e.g., human leukocyte antigen [HLA] susceptibility loci, cytotoxic T-lymphocyte antigen-4 [CTLA-4] genes) underpin the apparent diversity in TAO clinical features between different ethnicities.[16] However, extensive searches of medical literature databases revealed no data regarding Afro-Caribbean ethnicity and TAO nor data examining the relationship between socioeconomic status and TAO. The aim of this study was therefore to investigate the relationship between ethnicity, social grade, and level of social deprivation with TAO severity.

METHODS

Retrospective case note review of all patients seen for TAO at Birmingham and Midland Eye Centre (BMEC), United Kingdom, between

TABLE 1 Severity of TAO as defined by the European Group on Graves' Orbitopathy (EUGOGO).[2]

EUGOGO severity	Description
Mild	Patients with TAO that does not have a major impact on their life and therefore does not require medical or surgical treatment
Moderate-to-severe	Patients without sight-threatening TAO, but with disease that affects their everyday existence to an extent sufficient to warrant immunosuppressive treatment (if features of active TAO are manifest) or surgical rehabilitation (if there are no features of active TAO)
Sight-threatening	Patients who require urgent medical or surgical intervention for dysthyroid optic neuropathy (DON) or corneal compromise (with, e.g., intravenous glucocorticoid or urgent orbital decompression surgery)

TABLE 2. National Readership Survey social grade classification with percentage of the United Kingdom population (2010) represented in each grade.[17]

Social grade	Description	% Population
A	Higher managerial, administrative, and professional	4
B	Intermediate managerial, administrative, and professional	22
C1	Supervisory, clerical and junior managerial, administrative, and professional	29
C2	Skilled manual workers	21
D	Semi-skilled and unskilled manual workers	15
E	State pensioners, casual and lowest grade workers, unemployed with state benefits only	8

January 1998 and March 2012. A diagnosis of TAO was made according to clinical examination (presence of upper or lower eyelid retraction, exophthalmos, inflammatory signs of the ocular and periocular tissues, and restrictive myopathy), deranged thyroid function tests (TFTs), presence of thyroid autoantibodies, and radiologic signs (enlargement of extraocular muscles or orbital fat). Institutional review board was waived for this study.

A minimum period of follow up of 2 years (or definitive discharge from ophthalmic care) was stipulated to capture the full period of TAO inflammatory activity and consequent medical and surgical interventions. Note was taken of documented ethnicity—White (White-British, White-Irish, and White-Other), Asian (Indian, Pakistani, and Bangladeshi), or Black (African or Caribbean). Residence postcode was used to determine National Readership Survey (NRS) social grade and the level of social deprivation according to Index of Multiple Deprivation 2007 (IMD 2007).

The NRS classification is a demographic system of social grade classification based on the occupation of the chief income earner of the household and has been used since the 1960s (Table 2).[17] IMD 2007 is a well-validated indicator of social deprivation that integrates 7 "domains" of deprivation (income, employment, health deprivation and disability, educational skills and training, barriers to housing and services, crime, and living environment) that are combined, with appropriate weighting, in a single, overall deprivation score and ranking for each geographical area.[9]

For all analyses related to social grade, the 6 NRS classifications were abbreviated to 3 (A&B, C1&C2, and D&E). For all analyses related to social deprivation, TAO patients were ranked from lowest (least deprived) to highest (most deprived) score and divided into West Midlands-specific IMD 2007 quintiles, with quintile 1 the least deprived and quintile 5 the most deprived.

The measures chosen to define EUGOGO "moderate-to-severe" TAO were need for treatment with oral (prednisolone) or intravenous steroid (methylprednisolone), need for long-term immunosuppressant treatment (e.g., azathioprine, methotrexate, or ciclosporin), and need for orbital radiotherapy. The markers chosen to determine EUGOGO "sight-threatening" TAO were the presence of DON (clinically or on electrodiagnostic testing) and the need for urgent orbital decompression surgery for DON. In addition, the authors analyzed for influence on whether patients had evidence of active TAO (defined as a Clinical Activity Score [CAS] of ≥3) at the time of original presentation.

One-way analysis of variance (ANOVA) (with Bonferroni post hoc test) was used to compare age, Fisher exact test was used to compare proportions of all other demographic factors, and TAO severity markers in each ethnic group, social grade, and IMD 2007 quintile. Chi-square test compared the frequency of TAO patients observed in each West Midlands IMD 2007 quintile with the frequency expected. Multivariable logistic regression was then performed to simultaneously measure the influence (in the form of odds ratios [OR]) of a number of independent variables–age, gender, cigarette smoking status, NRS social grade, IMD 2007 deprivation quintile, and ethnicity—on markers of TAO severity as determined by the EUGOGO severity classification. Data were analyzed by using SPSS version 18 (IBM, Chicago, IL). $p \leq 0.05$ was considered statistically significant.

RESULTS

Three hundred and forty-three TAO patients were seen during the study period. Complete medical records of at least 2 years follow up were available for 273 (80%) of these. Mean age (SD) was 49 ± 14 years (range 17–87 years), with 74% (201/273) women, 72% (196/273) aged >40 years at time of presentation, and 36% (99/273) smokers. Of all TAO subjects, 77% (210/273) were of White ethnic origin, 12% (32/273) Asian, and 11% (31/273) Black. Two patients, each of White ethnic origin, had postcodes for which it was not possible to gain an IMD 2007 score and were therefore not included in these analyses. No patients were of East Asian (Chinese, Japanese, Korean, and Taiwanese) ethnic origin.

White subjects were significantly older than Asian and Black TAO subjects (mean age 51 years vs 42 and 43 years; $p < 0.0001$ and $p < 0.001$, respectively). White patients were more likely to be in social grade A&B than Asian or Black individuals (27% vs 16% and 10%, respectively; $p = 0.04$) and were also more likely to be in the least deprived quintile 1 (17% vs 3% and 0%, respectively; $p = 0.04$) and less likely to be in the most deprived quintile (22% vs 44% and 55%, respectively, $p = 0.01$). Furthermore, White subjects were more likely to smoke (40% vs 31% and 16%, respectively; $p = 0.01$) and be women (78% vs 56% and 61%, respectively; $p = 0.01$).

Chi-square comparison of the TAO patient frequency in each of the West Midlands IMD 2007 quintiles with the expected frequency of one-fifth in each quintile determined that there was statistically significant overrepresentation of TAO patients with higher levels of deprivation than that predicted from the reference population ($p < 0.0001$) (Table 3).

TABLE 3. Frequency of Index of Multiple Deprivation 2007 values by quintile in patients with thyroid-associated ophthalmopathy as compared with expected frequency in the population

Deprivation, quintile	West Midlands IMD 2007 score	TAO patients, in quintile	Expected frequency
1 (Least deprived)	1.33–10.07	37 (14%)	54.2
2	10.08–16.34	36 (13%)	54.2
3	16.35–25.07	47 (17%)	54.2
4	25.08–40.62	74 (27%)	54.2
5 (Most deprived)	40.63–80.34	77 (28%)	54.2
Total		271	271

$X^2 = 29.4$; df = 4; $p < 0.0001$.
IMD, index of multiple deprivation; TAO, thyroid-associated ophthalmopathy.

TABLE 4. Multivariable logistic regression analysis for the influence (in the form of odds ratios) of independent variables on markers of severe thyroid-associated ophthalmopathy, including social grade.

Variable	IV Steroid	Oral steroid	Radiotherapy	Immunosuppression	DON	Decompression	CAS≥3
Age							
≤40 y	1.0	1.0	1.0	1.0	1.0	1.0	1.0
>40 y	4.7 (1.8–12.4) $p = 0.002$	3.7 (1.8–7.6) $p < 0.0001$	3.6 (0.8–17.4) $p = 0.1$	9.6 (1.2–77.7) $p = 0.03$	6.9 (2.0–24) $p = 0.002$	3.3 (0.9–12.0) $p = 0.07$	3.4 (1.5–7.5) $p = 0.003$
Gender							
Female	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Male	1.0 (0.5–2.0) $p = 0.9$	1.0 (0.5–1.8) $p = 1.0$	1.8 (0.7–4.9) $p = 0.3$	0.2 (0.05–1.0) $p = 0.05$	0.7 (0.3–1.5) $p = 0.3$	0.6 (0.2–1.7) $p = 0.3$	1.2 (0.6–2.3) $p = 0.6$
Smoking							
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	1.4 (0.7–2.7) $p = 0.3$	1.6 (0.9–2.9) $p = 0.09$	2.0 (0.7–5.4) $p = 0.2$	2.7 (1.0–7.4) $p = 0.05$	1.3 (0.6–2.6) $p = 0.5$	0.8 (0.3–2.0) $p = 0.6$	2.0 (1.1–3.8) $p = 0.02$
Ethnicity							
White	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Asian	2.4 (0.9–6.5) $p = 0.08$	1.4 (0.6–3.3) $p = 0.5$	1.2 (0.2–6.5) $p = 0.8$	3.0 (0.7-13.0) $p = 0.1$	1.3 (0.4–4.4) $p = 0.6$	0.4 (0.05–3.7) $p = 0.4$	2.8 (1.1–7.0) $p = 0.03$
Black	1.1 (0.4–3.2) $p = 0.8$	0.9 (0.4–2.2) $p = 0.8$	1.7 (0.4–7.0) $p = 0.5$	0.9 (0.1–7.8) $p = 0.9$	1.5 (0.5–4.4) $p = 0.4$	2.3 (0.7–7.3) $p = 0.1$	1.2 (0.4–3.2) $p = 0.7$
NRS social grade							
A & B	1.0	1.0	1.0	1.0	1.0	1.0	1.0
C	1.7 (0.7–4.5) $p = 0.3$	2.1 (1.0–4.5) $p = 0.05$	2.2 (0.4–11.1) $p = 0.3$	2.5 (0.6–9.9) $p = 0.2$	3.0 (1.0–9.7) $p = 0.06$	2.4 (0.5–12.4) $p = 0.3$	1.7 (0.7–3.8) $p = 0.2$
D & E	2.6 (1.0–7.0) $p = 0.04$	2.3 (1.1–5.1) $p = 0.03$)	2.5 (0.5–12.7) $p = 0.3$	1.3 (0.3–5.7) $p = 0.8$	4.0 (1.2–12.7) $p = 0.02$	4.5 (0.9–21.6) $p = 0.06$	1.6 (0.7–3.7) $p = 0.3$

European Group on Graves' Orbitopathy (EUGOGO) definitions of moderate-to-severe TAO are indicated in light gray and sight-threatening in dark gray.
CAS, Clinical Activity Score; DON, dysthyroid optic neuropathy; IV, intravenous; NRS, National Readership Survey.

Overall, the rate for the need for treatment with oral steroid was 33% (89/273), intravenous steroid 19% (53/273), immunosuppressants 8% (21/273), and orbital radiotherapy 7% (19/273). Rates of DON were 16% (43/273) and orbital decompression 9% (25/273). Univariable comparison of the frequency of these measures of TAO severity between different ethnicities, NRS social grades, and IMD 2007 social deprivation scores revealed increased proportions of patients requiring oral ($p = 0.02$) and intravenous steroid ($p = 0.03$), having DON ($p = 0.01$) and requiring orbital decompression ($p = 0.04$) in social grades D&E as compared with social grades A&B. Except for the requirement for orbital decompression, this was replicated in analyses related to IMD 2007. However, there were no significant differences related to ethnicity.

Multivariable logistic regression demonstrated association between lower social grade (NRS D&E) and higher social deprivation scores (quintile 4) and increased odds of the presence of indicators of severe TAO, including need for treatment with oral and intravenous steroid, and the presence of DON, compared with those of highest social grade (NRS A&B) and lowest social deprivation scores (quintile 1). However, once again ethnicity had no independent association with any measure of TAO severity (Tables 4 and 5).

DISCUSSION

This study demonstrates independent associations between lower social grade and higher social deprivation and statistically significant increased odds of features associated with more severe TAO, as compared with those of higher social grade and lower levels of social deprivation. No such association was observed for ethnicity for any of the severity indices evaluated.

There are a number of possible explanations for such associations. Socioeconomic deprivation, as defined by not being in paid employment, has been found to be associated with nonattendance at hospital out-patient clinics.[18] This could have been the case for crucial endocrine and ophthalmic follow-up appointments for those TAO subjects of lower social grade or higher levels of deprivation. These patients may also have presented later to medical care or had higher rates of nonadherence with treatment modalities. Dietary factors may also have been important. An "oxidative stress" model of TAO postulates that hypoxia related, for example, to smoking, results in production of free radicals, which stimulate orbital fibroblast proliferation, glycosaminoglycan production, and orbital tissue expansion. It may be the lower consumption of antioxidants (in fruit and vegetables) in those of lower social grade or higher social deprivation that increases tendency to more severe TAO.[19]

We observed more definite independent associations of social position on TAO severity indices by using the NRS social grading rather than IMD 2007. IMD 2007 is a multifaceted measure of the level of social deprivation, encompassing a wide range of different issues of social disadvantage, not only financial. It is therefore likely to be the more robust method of analysing the influence of lower social status on disease than NRS, which measures only the occupation of the chief income earner of the household. However, IMD 2007 measures only deprivation within a postcode, not affluence. Not every person within a deprived area will necessarily be deprived. Likewise, there may be disadvantaged people living in the least deprived areas. In addition, we could not take account of social mobility over the 14-year period of the study. The postcode at the time of original clinic attendance was used to define the social status of each individual. However, it is possible that a number of patients moved between social strata over the study period.

To minimize this possible confounding factor, we used IMD 2007 rather than the more up-to-date IMD 2010. IMD 2007 is mostly based on data gained from 2004 to 2006, which were believed to be more equidistant between the start and end dates of data collection. Between IMD 2007 and IMD 2010, 63 TAO patients' postcode (23%) had a change in IMD score, with

TABLE 5. Multivariable logistic regression analysis for the influence (in the form of odds ratios) of independent variables on markers of severe thyroid-associated ophthalmopathy, including social deprivation.

Variable	IV steroid	Oral steroid	Radiotherapy	Immunosuppression	DON	Decompression	CAS≥3
Age							
≤40 y	1.0	1.0	1.0	1.0	1.0	1.0	1.0
>40 y	4.3 (1.6–11.2) $p = 0.003$	3.4 (1.7–7.1) $p = 0.001$	3.6 (0.7–17.5) $p = 0.1$	9.0 (1.3–69.2) $p = 0.04$	6.6 (1.9–22.9) $p = 0.003$	3.7 (1.0–13.5) $p = 0.05$	3.1 (1.4–7.1) $p = 0.007$
Gender							
Female	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Male	1.0 (0.5–2.0) $p = 0.9$	1.0 (0.6–2.0) $p = 0.9$	2.0 (0.7–5.7) $p = 0.2$	0.2 (0.05–0.9) $p = 0.04$	0.7 (0.3–1.6) $p = 0.4$	0.6 (0.2–1.8) $p = 0.4$	1.3 (0.6–2.5) $p = 0.5$
Smoking							
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	1.3 (0.7–2.6) $p = 0.4$	1.6 (0.9–2.7) $p = 0.1$	1.9 (0.7–5.2) $p = 0.2$	2.4 (1.1–6.5) $p = 0.05$	1.3 (0.6–2.6) $p = 0.5$	0.9 (0.3–2.2) $p = 0.7$	1.8 (1.0–3.4) $p = 0.05$
Ethnicity							
White	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Asian	1.9 (0.7–5.3) $p = 0.2$	1.1 (0.4–2.7) $p = 0.9$	1.2 (0.2–6.5) $p = 0.8$	2.7 (0.8–11.5) $p = 0.2$	1.0 (0.3–3.5) $p = 1.0$	0.4 (0.04–3.0) $p = 0.4$	2.3 (0.9–5.7) $p = 0.09$
Black	1.1 (0.4–3.2) $p = 0.9$	0.9 (0.3–2.2) $p = 0.7$	1.3 (0.3–6.1) $p = 0.7$	0.9 (0.2–7.0) $p = 0.8$	1.4 (0.5–4.3) $p = 0.5$	2.1 (0.6–7.0) $p = 0.2$	1.0 (0.4–2.7) $p = 1.0$
IMD 2007 Quintile							
1 (least deprived)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2	2.8 (0.9–8.7) $p = 0.07$	2.8 (1.1–6.8) $p = 0.03$	2.5 (0.5–13.6) $p = 0.3$	1.6 (0.4–4.3) $p = 0.2$	1.6 (0.5–5.2) $p = 0.5$	0.6 (0.1–3.6) $p = 0.5$	4.2 (1.4–12.7) $p = 0.01$
3	1.7 (0.5–5.8) $p = 0.4$	1.5 (0.6–3.8) $p = 0.4$	1.5 (0.2–9.8) $p = 0.7$	1.5 (0.7–3.9) $p = 0.7$	1.2 (0.3–4.5) $p = 0.7$	1.7 (0.4–7.8) $p = 0.5$	2.2 (0.7–7.2) $p = 0.2$
4	3.3 (1.1–10.4) $p = 0.04$	3.5 (1.4–8.7) $p = 0.008$	1.2 (0.2–7.7) $p = 0.9$	2.5 (0.8–5.2) $p = 0.7$	3.1 (1.0–10) $p = 0.05$	2.4 (0.5–10.7) $p = 0.2$	3.2 (1.0–10.1) $p = 0.04$
5 (most deprived)	2.4 (0.7–8.2) $p = 0.1$	2.4 (0.9–6.4) $p = 0.07$	2.4 (0.4–14.7) $p = 0.3$	1.8 (0.7–6.4) $p = 0.4$	2.2 (0.6–7.7) $p = 0.2$	3.1 (0.7–13.8) $p = 0.1$	3.5 (1.1–11.3) $p = 0.03$

CAS, Clinical Activity Score; DON, dysthyroid optic neuropathy; IMD, Index of Multiple Deprivation 2007; IV, intravenous.

62 of these moving down a quintile in a more deprived group. Nevertheless, reanalysis of the data by using IMD 2010 demonstrated similar results to those by using IMD 2007.

It was necessary to undertake the statistical method of multivariable logistic regression as the White population differed so significantly from the Asian and Black populations in important demographic factors such as age, gender, and smoking status. The direct statistical comparison of the proportions of each social or ethnicity group having each indicator of severe TAO is subject to confounding due to these inherent differences. By undertaking multivariable logistic regression, we aimed to "pick apart" the different factors known to influence TAO development and gain an independent measure for each (Supplemental Digital Content, Tables 1 and 2, http://links.lww.com/IOP/A77).

One of the most striking features of the data is that those aged greater than 40 years had increased odds of more severe TAO than those aged 40 years or less. Studies have already determined that there is an association between the severity of TAO and increased age and male gender.[15,20] However, smoking is the risk factor that has been most consistently associated with the development and severity of TAO, with those who stop smoking for at least a year having a risk equivalent to never smokers.[14,21] In other studies, more than 40% of smokers either developed or had worsening of TAO, almost double the rate of nonsmokers.[21] It is therefore surprising that the authors' study found few associations between smoking and severe TAO. There are a number of possible reasons for this. Although the statistical model incorporated a measure of whether each TAO patient smoked cigarettes at their original presentation, we did not classify patients by number of cigarettes smoked per day. In addition, smoking status may have been underreported, and it was also not possible to determine whether the rate of smoking cessation following presentation with TAO, or the passive smoking rate, differed in those of different social status or ethnicity.

It may be argued that further independent risk factors for severe TAO should be incorporated in the multivariable logistic regression model. For example, the duration of underlying autoimmune thyroid disease, thyroid autoantibody status, stability of TFTs, and previous treatment with radioactive iodine may also have had a significant contribution to the onset or worsening of TAO.[22,23] These data were not available for incorporation in the analysis.

In conclusion, this is the first study to consider the independent influence of social grade, level of social deprivation, and ethnicity on TAO severity in a large cohort of patients from a diverse, multiethnic population. In this cohort, we have illustrated that increased age, lower social grade, and higher social deprivation, but not ethnicity, have statistically significant association with some markers of severe TAO. Future studies should investigate further the influence of social factors and ethnicity on aspects of TAO presentation, treatment burden, prognosis, and the complex mechanisms underpinning these.

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