The Relationship Between Social Deprivation, Disease Outcome Measures, and Response to Treatment in Patients with Stable, Long-Standing Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Patients with rheumatoid arthritis (RA) with lower socioeconomic status (SES) are known to have more severe disease, more comorbidity, and higher mortality. It is not known whether SES influences response to treatment in RA. We examined the relationship between area of residence (as a surrogate for SES) and baseline outcome measures and response to treatment, using data from the British Rheumatoid Outcome Study Group randomized controlled trial of aggressive versus symptomatic treatment of long-standing, stable RA.

Methods. A total of 466 patients from 5 centers were recruited to the trial. Baseline data included age, sex, smoking status, and comorbidity. Patients were assigned a Townsend score (a measure of social deprivation) according to their area of residence. Outcome measures including the Disease Activity Score (DAS28), Health Assessment Questionnaire, Medical Outcomes Study Short Form-36, and EuroQol (EQ5D) were recorded at the beginning and end of the 3 year trial. The baseline, 3 year values, and change data were examined by Townsend quintile adjusting for each treatment arm.

Results. Significant relationships between increasing social deprivation by area of residence and higher disease activity, higher pain, poorer physical function, poorer emotional aspects of mental health, and lower quality of life were found at baseline (adjusted for age, sex, disease duration, current smoking, treatment center, and treatment group). During the 3 year trial period, patients from the most deprived areas showed greater improvement, with statistically significant greater improvement on DAS28 ($p = 0.041$) and 28 tender joint count ($p = 0.015$).

Conclusion. Area of residence is related to the severity of RA at recruitment and is a predictor of response in a clinical trial situation. The results suggest that measures of SES should be recorded for patients enrolled in clinical trials, longitudinal observational studies, and in the clinical setting. (J Rheumatol 2005;32:2330–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
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There is some evidence that social class and socioeconomic status (SES) may influence the course of rheumatoid arthritis (RA). Patients with RA with lower levels of education or from areas of social deprivation in the USA and UK have higher levels of comorbidity[1] and mortality[1,2]. They also have a worse outcome from their RA as measured by laboratory markers and physical function[3-7]. The influence of SES is thought to lessen as the disease progresses[5]. Relatively little is known about the influence of SES on health related quality of life (HRQOL) in RA. Studies of health status measured using activities of daily living along with visual analog scales (VAS) of pain, or HRQOL, suggest

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that SES influences perception of quality of life in RA, although the direction is unclear[1,3,5,7]. It is also unclear how SES influences the course of RA. Lifestyle factors of smoking and obesity alone do not explain the effect[8]. Evidence that the consultation behavior of patients with RA may vary between socioeconomic groups is conflicting[7,9,10].

Randomized controlled trials (RCT) inform us of the best treatment for the "average" RA patient satisfying the entry criteria. However, within all trials some patients are responders and some nonresponders. Most RCT lack power to explore predictors of response, yet this is essential information for treating individuals. Possible predictors of response include SES as well as other demographic factors, genetic factors, and disease-specific factors[11].

The British Rheumatoid Outcome Study Group (BROSG) RCT collected data on area of residence (as a surrogate for SES), baseline disease activity, physical function, health status, and HRQOL. Although OMERACT recommends that RCT in RA should include outcome measures for all these dimensions[12], relatively few RCT, to date, have done so. Therefore the BROSG trial provides an important dataset in which to explore the influence of SES on response to treatment.

MATERIALS AND METHODS

The study used the baseline and 3 year data of a large RCT of symptomatic versus aggressive therapy in patients with stable, long-standing RA. The trial was conducted in 5 geographically dispersed rheumatology centers in England (Stoke on Trent; Cannock Chase; Truro; King's College Hospital, London; and Macclesfield), which include teaching and district general hospitals, serving urban and rural populations.

Patients and methods. The BROSG Trial was conducted between 1998 and 2001[13,14]. The aim was to compare the relative clinical and cost-effectiveness and utility of symptomatic and aggressive treatment for established RA in a randomized, controlled, observer-blinded trial. Symptomatic-care patients were seen at home by a rheumatology specialist nurse every 4 months and annually by a rheumatologist, with the aim of controlling symptoms. Aggressive-care patients were seen at least every 4 months in hospital and treatment was altered (following predefined algorithms) with the aim of suppressing joint inflammation. Briefly, patients with RA defined using the 1987 American College of Rheumatology criteria[15] with disease of more than 5 years' duration were screened and invited to participate if they had been rheumatology outpatient attenders for at least 12 months, had been on stable therapy for at least 6 months, and had no evidence of systemic rheumatoid disease or serious comorbidity. The maximum dose of steroids permitted at enrolment was 7.5 mg daily. The primary outcome measure was change in physical function, measured using the British version of the Health Assessment Questionnaire (HAQ)[16]. The HAQ measures functional disability, scores ranging from 0 (no disability) to 3 (severe disability). Patients with a baseline HAQ score > 2.5 were excluded. The BROSG trial showed no difference in the primary outcome measure (HAQ) between treatment arms[14].

Demographic data included age, sex, disease duration, smoking status, and comorbidity. The baseline measurements included the OMERACT core set of outcome measures for RA clinical trials[17]: a patient global assessment, physician global assessment, tender joint count, swollen joint count, HAQ, and laboratory assessment of disease activity [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)]. The DAS28 — a composite measure of RA disease activity that uses a 28 tender joint count, a 28 swollen joint count, the ESR, and the patient global assessment, was also calculated[18]. Patients also completed a VAS for pain. Radiographs of the hands and feet were taken and read by a single observer, a musculoskeletal radiologist, using the Larsen scoring system[19]. In addition, patients completed the Medical Outcomes Study Short Form-36 (SF-36)[20], an internationally validated generic health status measure, and the EuroQol (EQ5D)[21], a generic measure of health status and health related utility[22]. All measures were repeated at the end of the 3 year trial.

Comorbidity information was collected from patients and medical records at baseline. Conditions were grouped according to body system: cardiovascular disease (CVD) including hypertension, psychiatric including depression, respiratory, endocrine, gastrointestinal (GI), and the nervous system. Comorbidities that had resolved prior to the start of the trial were excluded.

A Townsend Index score (a measure of social deprivation based on area of residence)[23,24] was allocated to each patient on the basis of their postal code. Postal codes were matched to enumeration districts using the MIMAS website[25]. Townsend scores are assigned based on the enumeration district (approximate mean 200 households) in which an individual's postal code is located. The score uses a formula based on the log of unemployment (percentage of economically active persons aged ≥ 16 years that are unemployed), log of overcrowding (percentage of households with ≥ one person per room), non-car ownership (percentage of households not owning a car), and non-home ownership (percentage of households not owning their own house). The variables are standardized using z scores and summed to create the Townsend score. The mean Townsend score for England and Wales is 0 (SD 3.39)[23]. Negative scores indicate areas ranked as less deprived and positive scores areas more deprived than average. Townsend scores for England and Wales range from –7.55 to 11.8, and over 95% of scores lie within the mean ± 2 standard deviations. Each individual was then allocated to one of the Townsend quintiles for England and Wales.

Statistical analysis. All analyses were carried out using Stata version 8.2[26]. An extension of the Wilcoxon rank-sum test for trend was used to test trend across ordered Townsend quintiles at baseline, for change during followup, and after 3 years of followup. Analyses of change during followup and after 3 years' followup were restricted to those completing the trial.

A generalized least-squares random effects model was used to assess significant differences at baseline and change in outcome measures [adjusted for age, sex, disease duration, current smoking, treatment center, and treatment group (for the change analysis)] over the 3 years of the trial with respect to Townsend quintile. This tested whether change in a measure differed significantly by quintile of deprivation in its intercept (baseline measure) and gradient (rate of change) during the study. The model accounts for dropout by using all available data to calculate intercepts and gradients for defined groups.

RESULTS

A total of 466 patients were recruited to the trial. Three patients could not be allocated a Townsend score because of inaccurate postal code data. Baseline characteristics of the whole cohort are shown in Table 1. Centers differed significantly in age, Townsend score, and the EQ5D VAS (patient's perspective) component. Macclesfield served the least socially deprived and King's College London the most socially deprived areas. Although median Townsend scores varied between centers, the overall spread for trial participants combined was very similar to England and Wales (Figure 1). Townsend quintiles 1 and 2 were collapsed into a single category, as it was apparent from the data that no difference existed between these categories for the patients in the trial.

Median age, proportion of women, disease duration, or

Table 1. Baseline characteristics of trial participants and comparison by quintile of social deprivation (n = 466).

	Overall Median (IQR), n = 466	Townsend Quintile, median (IQR) 1 and 2, n = 201	3, n = 95	4, n = 86	5, n = 81	p
Demographics						
Age, yrs	62.1 (53.2, 69.3)	61.5 (53.3, 67.6)	62.8 (54.8, 70.3)	60.3 (51.5, 70.0)	63.9 (54.5, 69.9)	0.293
Female, n (%)	317 (68)	136 (68)	58 (61)	62 (72)	58 (72)	0.379
Disease duration, yrs	11 (7, 16)	11 (7, 17)	11 (8, 18)	10 (7, 16)	10 (7, 14)	0.219
Current smoker, n (%)	106 (23)	38 (19)	24 (26)	19 (22)	25 (32)	0.044
Disease activity						
DAS28	4.0 (3.2, 4.9)	4.0 (3.1, 4.8)	3.8 (3.0, 4.6)	4.0 (3.4, 5.0)	4.7 (3.5, 5.2)	0.002
28 tender joint count	3 (1, 7.5)	3 (0.5, 7)	2.5 (0, 6)	3 (1, 8)	6 (2, 11)	< 0.001
28 swollen joint count	3 (0, 6)	3 (1, 6)	3 (0.5, 5)	3 (1, 7)	4 (1, 7)	0.157
Patient global assessment	34 (23, 49)	35 (24, 49.5)	31 (21, 46)	32 (23, 48)	37.5 (27, 52)	0.384
Erythrocyte sedimentation rate	19 (10, 32)	18 (9, 30)	17.5 (9, 34)	19 (10, 33)	20 (10, 30)	0.242
Pain VAS	44 (22, 60)	40.5 (20, 53.5)	48 (23, 65)	40 (20, 61)	48.5 (34, 66)	0.011
Radiographic assessment						
Larsen score	67 (42, 96)	67 (47, 93)	71 (38, 102)	63.5 (42, 93)	66 (30, 106)	0.783
Eroded joint count	11 (5, 18)	11 (6, 17)	11 (6, 20)	11 (6, 17)	11 (2, 20)	0.776
Physical function						
HAQ	1.4 (0.8, 1.9)	1.25 (0.63, 1.75)	1.25 (0.50, 1.88)	1.38 (0.88, 2.0)	1.63 (1.13, 2.0)	< 0.001
SF-36						
Physical composite score	31.0 (24.5, 38.7)	31.3 (24.5, 39.9)	32.2 (25.0. 38.8)	31.2 (23.8, 39.7)	28.7 (23.4, 34.2)	0.054
Mental composite score	52.3 (42.7, 58.9)	52.9 (43.9, 58.8)	53.9 (43.3, 60.8)	52.2 (42.7, 59.1)	47.0 (35.4, 55.7)	0.001
EQ5D						
Utility	0.6 (0.5, 0.7)	0.62 (0.53, 0.73)	0.59 (0.52, 0.73)	0.62 (0.52, 0.76)	0.59 (0.52, 0.66)	0.011
VAS	64.5 (50, 80)	66 (51, 80)	60 (50, 80)	70 (60, 80)	60 (50, 71)	0.107

HAQ: Health Assessment Questionnaire, SF-36: Medical Outcome Study Short Form-36, EQ5D: EuroQol[21], VAS: visual analog scale score, IQR: interquartile range.

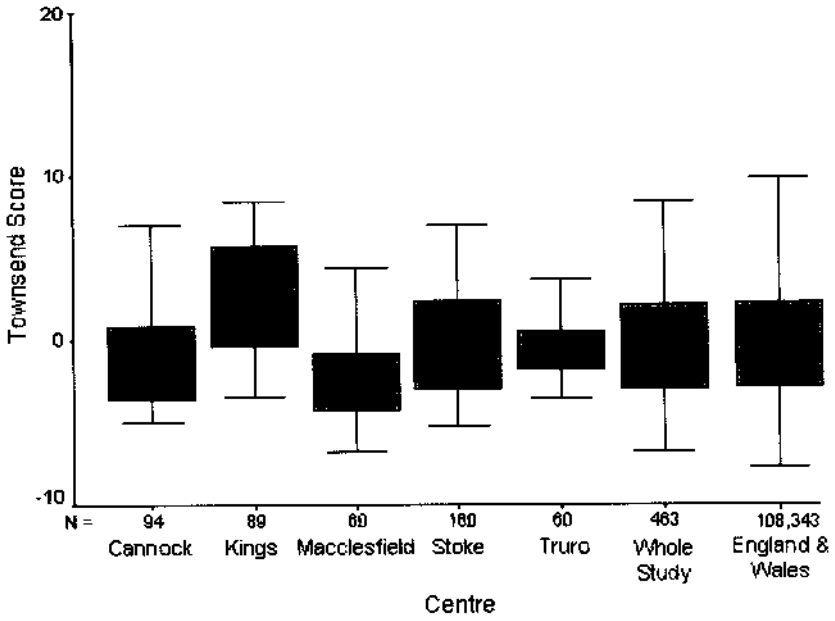

Figure 1. Townsend score of social deprivation for individual centers in this study, the whole BROSG study, and England and Wales combined.

treatment allocation did not differ between Townsend quintiles (Table 1). More patients in Townsend quintile 5 (most deprived) smoked (32%) than in quintiles 1 and 2 (19%; p = 0.044). The DAS28, 28 tender joint count, VAS for pain, HAQ, SF-36 mental component score, and the EQ5D utility score all worsened significantly with area of increasing social deprivation. The association between the DAS28 and Townsend quintile seems to be driven by the 28 tender joint

count. There was no association between social deprivation and the ESR or swollen joint count, nor with radiographic damage or the EQ5D VAS of HRQOL. Treatment at baseline did not differ between Townsend quintiles (Table 2).

A total of 406 (87%) patients completed the trial. The numbers of patients lost to followup (n = 15) or dying (n = 17) during the study period did not differ significantly between Townsend quintiles, although the numbers of patients withdrawing from the study (n = 28) did (p = 0.016; Table 3). Fewer patients from more socially deprived areas attended for their 3 year radiograph (p = 0.004).

The median 28 tender and swollen joint counts improved for patients in all quintiles during the trial (Table 4). All other outcomes either remained unchanged or deteriorated, except the VAS for pain, which improved only in the most deprived quintile.

The random effects analysis took into account dropout and loss to followup, which varied between Townsend quintiles (Table 5). The intercepts, equivalent to baseline scores, for DAS28 (p = 0.003), 28 tender joint count (p < 0.001), VAS for pain (p = 0.002), HAQ (p < 0.001), SF-36 mental component score (p = 0.002), SF-36 physical component score (p = 0.001), and EQ5D utility (p = 0.001) measures consistently showed significant linear relationships of poorer baseline scores in more deprived quintiles, adjusted for age, sex, disease duration, current smoking, treatment center, and treatment group. The linear relationships were oversimplifications of the results, which could be isolated to a threshold effect for the 2 most deprived quintiles for DAS28 (coefficient 0.352, p = 0.002), 28 tender joint count (coefficient 1.771, p = 0.001), and EQ5D utility (coefficient –0.068, p = 0.001) and the most deprived for SF-36 mental component score (coefficient –3.911, p = 0.002) compared to the remainder. The association between HAQ and area of residence remained significant (p < 0.001) when further adjusted for EQ5D utility. In contrast, the association with the EQ5D utility was lost after further adjustment for HAQ. The adjusted increase in HAQ score of 0.129 for each quintile increase in Townsend score equates to a mean difference in HAQ score of 0.52 across the quintiles of the Townsend score.

Significant differences in the rate of change over the 3

Table 2. Number of patients undergoing DMARD treatments, combinations of DMARD, or steroids at baseline for the overall group and by quintile of social deprivation (n = 466).

	Overall, n = 466	Townsend Quintile 1 and 2, n = 201	3, n = 95	4, n = 86	5, n = 81	p
DMARD						
Auranofin	9	2	3	2	2	
Azathioprine	7	1	0	1	4	
Cyclosporine	1	1	—	—	—	
Intramuscular gold (myocrisin)	33	15	4	7	7	
Hydroxychloroquine	15	8	2	1	4	
Methotrexate	75	30	21	11	13	0.761
Penicillamine	35	17	9	4	5	
Sulfasalazine	124	48	27	25	23	0.282
At least one DMARD	275	113	63	44	53	0.414
Combination of DMARD	24	9	3	7	5	
Steroid						
Hydrocortisone	1	—	—	—	1	
Prednisolone	30	10	7	4	9	
Any steroid	31	10	7	4	10	

DMARD: disease modifying antirheumatic drug.

Table 3. Deaths, loss to followup, and radiographs for the trial group and in relation to quintile of social deprivation (n = 466).

	Overall, n (%)	Townsend Quintile, n (%) 1 and 2,	3,	4,	5,	p
N at baseline	466	201	95	86	81	
Died	17 (4)	6 (3)	5 (5)	3 (3)	3 (4)	0.783
Lost to followup	15 (3)	3 (1)	5 (5)	3 (3)	4 (5)	0.138
Withdrawn	28 (6)	7 (3)	6 (6)	6 (7)	9 (11)	0.016
No baseline radiograph	60 (13)	26 (13)	12 (13)	12 (14)	10 (12)	0.991
No 36 month radiograph	109 (23)	36 (18)	23 (24)	23 (27)	27 (33)	0.004

Table 4. Change in outcome measures during the study period and comparison of change by quintile of social deprivation (n = 406). Values have been recoded so that positive values denote improvement and negative values deterioration.

	Overall Median (IQR), n = 406	Townsend Quintile, median (IQR) 1 and 2, n = 185	3, n = 79	4, n = 74	5, n = 65	p
Disease activity						
DAS28	0.02 (–0.8, 0.8)	–0.1 (–0.8, 0.8)	0.2 (–0.7, 0.8)	–0.1 (–0.8, 0.6)	0.7 (–0.6, 1.3)	0.109
28 tender joint count	0 (–2, 3)	0 (–2, 2)	1 (–2, 2)	0 (–3, 2)	1.5 (–1.5, 4.5)	0.125
28 swollen joint count	1 (–1, 4)	0 (–1, 3)	1 (–1, 4)	0 (–2, 3)	3 (–1, 5)	0.050
Patient global assessment	2 (–10, 19)	1 (–9, 16)	3 (–8, 16)	6 (–12, 20)	5 (–11, 20)	0.542
Erythrocyte sedimentation rate	0 (–8, 9)	0 (–8.5, 7)	–1 (–14, 9)	0 (–10, 6)	–0.5 (–7, 10)	0.704
Pain VAS	–3 (–20, 12)	–3 (–21, 13.5)	0 (–16, 12)	–9 (–25, 8)	3 (–19, 13)	0.903
Radiographic assessment						
Larsen-Dale score	–4 (–10, 0)	–5 (–11, 0)	–5 (–10, 0)	–3 (–10, 1)	–4 (–7, 0)	0.204
Eroded joint count	0 (–2, 0)	–1 (–2, 0)	0 (–1, 0)	0 (–2, 0)	–1 (–2, 0)	0.925
Physical function						
HAQ	–0.1 (–0.4, 0.1)	–0.1 (–0.4, 0.0)	–0.1 (–0.5, 0.0)	–0.1 (–0.4, 0.0)	–0.1 (–0.4, 0.1)	0.751
SF-36						
Physical component score	–1.2 (–6.1, 4.2)	–1.1 (–6.1, 4.6)	–0.7 (–5.7, 3.5)	–1.5 (–8.1, 4.5)	–0.8 (–5.5, 4.2)	0.747
Mental component score	–1.9 (–7.9, 4.0)	–2.4 (–8.0, 2.6)	–1.8 (–5.4, 6.9)	–1.7 (–9.2, 4.7)	–0.04 (–7.4, 5.7)	0.189
EQ5D						
Utility	0.00 (–0.10, 0.00)	0.00 (0.10, 0.00)	0.00 (–0.10, 0.00)	–0.04 (–0.12, 0.00)	0.00 (–0.10, 0.07)	0.978
VAS	–5 (–30, 8)	–8 (–36, 3)	–1.5 (–29, 10)	–4 (–20, 10)	–4 (–20, 12)	0.055

HAQ: Health Assessment Questionnarie, VAS: visual analog scale score, IQR: interquartile range.

Table 5. Differences in baseline score in outcome measure (intercept) and change throughout the study (gradient) presented as a linear function of deprivation quintile (n = 466), adjusted for age, sex, disease duration, smoking, treatment, and center.

	Intercept Coefficient	p	Gradient Coefficient	p
Disease activity				
DAS	0.161	0.003	–0.035	0.041
28 tender joint count	0.902	< 0.001	–0.185	0.015
Pain VAS	2.848	0.002	–0.278	0.431
Physical function				
HAQ	0.129	< 0.001	–0.002	0.688
SF-36				
Physical component score	–1.425	0.001	–0.042	0.708
Mental component score	–1.444	0.002	0.268	0.056
EQ5D				
Utility	–0.035	0.001	0.002	0.591

year followup were found across Townsend quintiles for DAS28 (p = 0.041) and the 28 tender joint count (p = 0.015). The linear effect was an oversimplification of an effect that could be isolated to a threshold of better outcome for the most deprived quintile compared to the remaining quintiles for the 28 tender joint count (coefficient –0.456, p = 0.035).

There was no significant relationship between the DAS28 and social deprivation at 3 years in those completing the trial, although the relationship with the 28 tender joint count remained significant (p = 0.047). The significant association between HAQ and area of residence also persisted at 3 years (p = 0.002), despite significant improvement in disease activity measures in those from the most deprived areas.

The prevalence of comorbidity was related to area of residence (p = 0.001). The trend was also significant for respiratory comorbidities (p = 0.038).

DISCUSSION

Our study found significant relationships between area of residence and measures of health and health status at baseline. The analyses in this study suggest that patients from more socially deprived areas are more likely to experience higher disease activity, poorer physical function, poorer emotional aspects of mental health, lower quality of life, and greater pain. These relationships persisted when adjusted for age, sex, disease duration, current smoking, center, and treatment group. The increased disability reported by those

from areas of greater social deprivation appeared to be the main factor affecting the quality of life reported by these patients. These findings support previous findings of poorer scores in more socially deprived patients for a number of clinical outcome measures[3-6,9,27].

Patients from more deprived areas appeared to benefit most from inclusion in the trial, although this was only significant for the DAS28 and 28 tender joint count. Pain appeared to be the driving factor in observed differences between the quintiles at baseline, and improvements in pain helped to reduce inequality in health status between Townsend quintiles during the trial. These significantly different gradients cannot be attributed to regression to the mean, as the random effects model compares the group means for the Townsend quintiles. Regression to the mean would occur within groups, therefore comparison of multiple group means would not be influenced by regression to the mean.

The outcome in the 2 arms of the trial did not differ significantly with regard to HAQ (the primary outcome measure). Adjustment for treatment did not attenuate the different gradients of change between groups defined by area of residence. Patients from more deprived areas enrolled in a clinical trial could benefit from participation by 3 possible mechanisms. First, they may be more compliant with drug routines and hospital appointments in a clinical trial situation than in routine practice. Although this trial was conducted within the National Health Service, which should offer universally standard treatment, patients may vary in ability to articulate problems and negotiate extra treatment according to their SES. This has been reported in the UK[6] and The Netherlands[5].

Second, closer monitoring and interest in the progression of the patient's disease may lead to a more positive and optimistic outlook in the patient. This could lead to improvements in general health and well being that are reflected in outcome measures, such as the EQ5D VAS (patient's perspective) and the SF-36 mental component score.

Third, patients in the more deprived quintiles also had higher levels of comorbidity, particularly respiratory conditions. It is possible that the health of these patients improved not only in terms of RA but also that their comorbidity benefited from closer scrutiny through inclusion in the trial. Improvements in comorbidity could influence outcome measures in this study, particularly those of health related quality of life and physical function.

The differential progression of disease in the trial reduced the cross-sectional trends of poorer outcome in groups of greater deprivation after 3 years of followup. The groups were then more closely matched, and the only remaining statistically significant trends across deprivation groups were the 28 tender joint count and the HAQ.

This study has a number of strengths. First, the study was based on a large group of patients with established RA socially representative of the England and Wales population[14]. The BROSG study collected all the outcome measures recommended (element 6) by the OMERACT reference case for RA[28] for a high quality and comparable study.

The study used the Townsend Index, a proxy measure of SES developed and validated for epidemiological studies in England and Wales. The Townsend Index has been reported to measure the material aspects of social deprivation[29,30]. The Townsend Index has been shown to provide results consistent with the measure of disposable income[29], and to correlate strongly with other measures of deprivation[30]. The Townsend Index has also been found to correlate with a number of measures of ill-health, most notably standardized mortality ratios[30-32], permanent sickness[30,32], and temporary sickness[30]. A wide variety of studies have employed the Townsend Index, including epidemiological studies of coronary heart disease mortality and prevalence of angina symptoms[33], epilepsy[34], orofacial pain[35], and dental disease[36].

A possible disadvantage of the study was that the Townsend Index was the only measure of SES used. Area-based measures may be subject to the "ecological fallacy" whereby relationships apparent at the aggregate level do not hold at the individual level. However, using the Townsend Index avoids the problems of measuring SES at the individual level in UK studies of RA. Measures of income are difficult to obtain in the UK as people are unwilling to disclose their income. Income and occupation measured in RA populations may be subject to confounding by spousal income (due to the predominance of women), and longterm sickness influencing the nature of employment and retirement age. Length of education is not a useful surrogate for SES, as the majority leave school as soon as they reach the maximum age for compulsory education.

The results of this study have shown, for the first time, that area of residence (as a marker of social deprivation) is a predictor of response in terms of disease activity in a clinical trial situation, and add to the literature reporting trends of poorer clinical status in RA patients from areas of greater social deprivation. These findings suggest that some measure of SES should always be collected for patients enrolled in clinical trials and longitudinal observational studies, and in the clinical setting. This suggestion is supported by the recent recommendations of Lee and Kavanaugh[37] for greater reporting of SES in clinical trials to assess external validity. Further areas of research include investigation of whether the influence of area of residence seen in this clinical trial is replicated in longitudinal observational studies, and exploration of what aspects of the concept of social deprivation lead to differential clinical outcome.

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