Costs in Relation to Disability, Disease Activity, and Health-related Quality of Life in Rheumatoid Arthritis: Observational Data from Southern Sweden

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ABSTRACT. ***Objective.*** To compare how costs relate to disability, disease activity, and health-related quality of life (HRQOL) in rheumatoid arthritis (RA).

Methods. Antitumor necrosis factor (anti-TNF)-treated patients with RA in southern Sweden (n = 2341) were monitored 2005–2010. Health Assessment Questionnaire (HAQ), 28-joint Disease Activity Score (DAS28), and EQ-5D scores were linked to register-derived costs of antirheumatic drugs (excluding anti-TNF agents), patient care, and work loss from 30 days before to 30 days after each visit (n = 13,289). Associations of HAQ/DAS28/EQ-5D to healthcare (patient care and drugs) and work loss costs (patients < 65 yrs) were studied in separate regression models, comparing standardized β coefficients by nonparametric bootstrapping to assess which measure best reflects costs. Analyses were conducted based on both individual means (linear regression, comparing between-patient associations) and by generalized estimating equations (GEE), using all observations to also account for within-patient associations of HAQ/DAS28/EQ-5D to costs.

Results. Regardless of the methodology (linear or GEE regression), HAQ was most closely related to both cost types, while work loss costs were also more closely associated with EQ-5D than DAS28. The results of the linear models for healthcare costs were standardized β = 0.21 (95% CI 0.15–0.27), 0.16 (0.11–0.21), and –0.15 (–0.21 to –0.10) for HAQ/DAS28/EQ-5D, respectively ($p < 0.05$ for HAQ vs DAS28/EQ-5D). For work loss costs, the results were standardized β = 0.43 (95% CI 0.39–0.48), 0.27 (0.23–0.32), and –0.34 (–0.38 to –0.29) for HAQ/DAS28/EQ-5D, respectively ($p < 0.05$ for HAQ vs DAS28/EQ-5D and for EQ-5D vs DAS28).

Conclusion. Overall, HAQ disability is a better marker of RA costs than DAS28 or EQ-5D HRQOL.
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Rheumatoid arthritis (RA) and its treatment inflict high costs on society[1,2]. For the clinician, knowledge of how different commonly used clinical measures reflect costs may therefore be helpful to better understand the full economic consequences of the disease, as well as to identify patients for whom extra care may be needed to avoid progression to work disability and/or stages with elevated healthcare needs.

The biologic era has inspired an increasing interest in cost-utility analyses, comparing the cost per quality-adjusted life-year (QALY) of different interventions[3,4]. Costs are traditionally identified by patient surveys[5,6], although recently, linkage with nationwide registers has offered a powerful alternative way to assess costs without the nonresponse and recall bias associated with questionnaires. Collection of economic data has, however, often been omitted in RA trials, and available cost-utility analyses have mostly applied costs (and QALY) indirectly calculated from other measures, such as the Health Assessment Questionnaire (HAQ) score[3,4,7,8]. The accuracy of such analyses is thus directly linked to the quality of the underlying data describing the relation between

costs and the surrogate measures, and up-to-date information on such relationships is therefore in demand.

HAQ disability is known to be strongly associated with both healthcare and work loss costs in RA[5,9–18]. Much less is known of how costs relate to disease activity or health-related quality of life (HRQOL), the former of interest not least because of the debate of whether to regard remission or low disease activity as the standard treatment target. A few studies have reported increased healthcare costs in higher 28-joint Disease Activity Score (DAS28) states[19,20,21], and HAQ and DAS28 were both found to predict work disability in one paper[18]. As measured by the EQ-5D[22,23], HRQOL has been shown to correlate to both healthcare and work loss costs at levels similar to HAQ[5,24].

Combining observational data from southern Sweden with costs from national registers, we aimed to describe and compare how disability (HAQ), disease activity (DAS28), and HRQOL (EQ-5D) relate to healthcare (patient care and antirheumatic drugs), work loss (sick leave and disability pensions), and societal costs (the sum of the previous) in antitumor necrosis factor (anti-TNF)-treated patients with RA.

MATERIALS AND METHODS

The Swedish healthcare system. Swedish healthcare is provided to all citizens by a common tax-funded system. Prescription drugs are free above an annual threshold, which during the study period amounted to 1800 SEK (≈$275). RA is managed by rheumatologists, the vast majority of whom work at public hospitals, and is centered on outpatient care. Sick leave and disability pensions are approved and administered by the Social Insurance Agency.

The South Swedish Arthritis Treatment Group Register (SSATG). Patients with RA who are receiving biologic disease-modifying antirheumatic drugs (DMARD) in southern Sweden were monitored in the observational SSATG register[25] involving 12 rheumatology centers. At each visit, scheduled at treatment initiation, 3, 6, and 12 months of followup, and then at least annually, HAQ disability, DAS28 disease activity, and EQ-5D HRQOL (using the original 3-level version of the EQ-5D questionnaire[26]) were recorded, along with other patient and disease characteristics, treatment information, and dosing. For the main analyses, EQ-5D utility scores according to the standard, hypothetical UK preference set were used[27], whereas results based on the experience-based Swedish preference set (EQ-5D-SE) are also provided in the online data supplement (available online at jrheum.org) for comparison[28].

Inclusion criteria. Patients with RA (≥ 18 yrs) receiving anti-TNF treatment (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol) from July 2005 to December 2010 were retrieved from the SSATG register. At least 1 HAQ, DAS28, or EQ-5D score recorded during this period was required for inclusion (n = 2341). Patients had a clinical RA diagnosis, although a previous validation study showed 98% of controlled cases to have fulfilled the 1987 American College of Rheumatology criteria[25,29]. Because the Swedish retirement age is 65 years, analyses including work loss costs (sick leave and disability pensions) were restricted to patients < 65 years (n = 1669; 71%).

Costs. Aiming to describe and compare the general associations of HAQ, DAS28, and EQ-5D to costs in anti-TNF–treated patients with RA, all available visits with valid data for any of these scores in the SSATG register during the study period were included, regardless of disease severity, previous treatments, time from diagnosis, or the start of anti-TNF therapy. For each included visit (all patients/patients < 65 yrs, n = 13,289/9047), costs of antirheumatic drugs, patient care, and work loss were calculated from 30 days before to 30 days after the visit (referred to as 60-day periods) using registry data. This time window was chosen to optimally reflect costs in conjunction with each visit, while limiting overlap between repeated measures in the same patient. All costs were converted to 2011 US dollars ($1 US = 6.50 SEK).

Antirheumatic drugs. Antirheumatic drug use and doses were retrieved from the SSATG register. Costs were calculated using 2011 listed drug prices in Sweden (www.tlv.se). Because of the inclusion criteria and the similar pricing of all TNF inhibitors, anti-TNF cost varied little between patients and was excluded from all analyses. The non-anti-TNF drug costs considered encompassed conventional DMARD, glucocorticoids, and nonsteroidal antiinflammatory drugs. For a few patients with severe disease (n = 8), costs of rituximab were also included when used in parallel with anti-TNF treatment.

Patient care. Inpatient (including surgery) and nonprimary outpatient (including day surgery) care data during each 60-day period were collected from the National Patient Register at the National Board of Health and Welfare[30]. Costs were calculated using the diagnosis-related group coding system, a weighted average of costs per disease group, from 2011 (www.socialstyrelsen.se).

Work loss. Day-level data on sick leave and disability pensions were retrieved from the Social Insurance Agency. Using the human capital method, work loss costs during each 60-day period were estimated as the accumulated days of sick leave and disability pension multiplied with the mean average salary per day, including social fees, in Sweden in 2011 (www.scb.se). Sick leave periods ≤ 14 days were not included in this cost calculation because they are compensated by the employer and are not systematically recorded by the Social Insurance Agency. If a new sick leave period started within 5 days of another, they were, however, counted together, and once exceeding 14 days, the first 2 weeks were also recorded (and thus included in our present cost calculation).

Non-anti-TNF healthcare costs. The description used below to denote healthcare (patient care plus antirheumatic drugs) costs, excluding costs of anti-TNF agents.

Non-anti-TNF societal costs. The description used below to denote societal (healthcare plus work loss) costs, excluding costs of anti-TNF agents.

Ethics. The quality control character of the SSATG register makes it part of the legislative documentation demanded in Sweden and no ethical approval was thus required for the collection or analysis of clinical variables. For the linkage to cost data from nationwide registers, ethical approval was granted by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden.

Statistics. The associations of HAQ, DAS28, and EQ-5D scores to the various cost types were studied by descriptive statistics, Spearman correlation, and regression analyses. Because of the varying number of visits per patient (range 1–59), individual means were used for the descriptive and correlation analyses. Regressions were conducted both based on individual patient means (linear regression) to compare between-patient associations of the 3 measures to costs, and by generalized estimating equations (GEE), including data from all visits to use all observations and also account for within-patient associations between the measures and costs. For transparency, in the online data supplement (available online at jrheum.org), all figures are reproduced based on data from all visits.

Descriptive. HAQ, DAS28, and EQ-5D scores were categorized (only for the figures, not for the correlation/regression analyses), and cost distributions were analyzed by bar charts and box plots. For DAS28, we used the pre-defined disease activity states (remission < 2.6, low ≥ 2.6 and ≤ 3.2, moderate > 3.2 and ≤ 5.1, and high > 5.1), while HAQ scores were categorized by intervals of 0.5, but retaining 0 as a separate category. EQ-5D scores (range –0.59 to 1.00) were divided into 7 categories: 1.00, 5 categories between 0.99 and 0.00 by intervals of 0.20, and all values < 0.00, the latter category wider because of few patients with mean utility < –0.20 (n = 14).

Spearman correlation. Correlations of HAQ, DAS28, and EQ-5D to the various cost types were calculated and compared by Fisher's r-to-z transformation[31].

Regression analyses. Associations of HAQ, DAS28, and EQ-5D to non-anti-TNF healthcare, work loss, and non-anti-TNF societal costs were studied in separate models, adjusting for age, sex, disease duration, previous number of biologics used, time from start of the present anti-TNF therapy, and followup calendar year. All assessments were conducted both by linear (using individual means for all variables) and GEE (all visits, applying exchangeable correlation structure) regression. Unadjusted analyses were also performed. Despite skewed cost distributions, residuals of the linear work loss and non-anti-TNF societal cost models were normally distributed (Shapiro-Wilk ≥ 0.95), whereas this was not the case regarding non-anti-TNF healthcare costs alone, mainly because of high kurtosis. To account for this, nonparametric bootstrapping was used to estimate CI in all models (both linear and GEE)[32]. To assess whether HAQ, DAS28, and EQ-5D scores differed significantly in their associations to the various cost types, bootstrapping with 1000 iterations was again applied. For each bootstrap sample, we thus calculated the difference between the standardized β coefficients for the 2 measures compared (i.e., for HAQ vs DAS28, HAQ vs EQ-5D, and DAS28 vs EQ-5D), thereby computing a 95% CI for this difference.

RESULTS

During the study period, 13,289 visits with valid HAQ, DAS28, and/or EQ-5D scores were recorded among 2341 anti-TNF–treated patients with RA in the SSATG register. Patient characteristics based on data from the first study visit of each subject are displayed in Table 1, while the mean/median 60-day costs are shown in Supplementary Table 1 (available online at jrheum.org). Skewed distributions were seen for HAQ, EQ-5D, and costs (Supplementary Figure 1 and Supplementary Figure 2, available online at jrheum.org). In Sweden, sick leave and disability pensions are approved for 25%, 50%, 75%, or 100% of the working time, explaining the multimodal distributions of work loss and societal costs. Overall, 57% of patients < 65 years were receiving disability pension at some level in conjunction with at least 1 visit, reflecting the advanced disease in this group of anti-TNF–treated subjects.

Worse levels of HAQ, DAS28, and EQ-5D were all associated with higher non-anti-TNF healthcare and work loss costs, the former mainly driven by greater needs for inpatient care (Figure 1 and Figure 2; Supplementary Figure 3 available online at jrheum.org). The presence of full-time work disability rose steeply with higher HAQ categories, while subjects with elevated disease activity or low HRQOL more frequently retained some working capacity (Supplementary Figure 5D available online at jrheum.org).

Correlations. Spearman correlations between the HAQ, DAS28, and EQ-5D scores were $r_s = 0.57$ for HAQ versus DAS28, –0.74 for HAQ versus EQ-5D, and –0.59 for DAS28 versus EQ-5D. All measures correlated more closely with

Table 1. Patient characteristics at first study visit. Values are n (%) unless otherwise specified.

Characteristics	All Patients, n = 2341	Missing Data	Patients < 65 Yrs, n = 1669	Missing Data
No. study visits				
Mean (SD)	5.7 (5.5)		5.4 (5.4)	
Median (IQR, range)	5 (4, 1–59)		4 (5, 1–59)	
Women	1789 (76)		1299 (78)	
Age, yrs, mean (SD)	57 (13)		51 (11)	
Education, yrs		61 (2.6)		44 (2.6)
≤ 9	698 (30)		399 (24)	
10–12	972 (42)		729 (44)	
> 12	610 (26)		497 (30)	
Disease duration, yrs		6 (0.3)		7 (0.4)
Mean (SD)	13 (11)		11 (9.3)	
Median (IQR, range)	10 (14, 0–67)		8.7 (12, 0–59)	
HAQ score		22 (0.9)		15 (0.9)
Mean (SD)	1.03 (0.68)		0.96 (0.63)	
Median (IQR, range)	1.00 (1.00, 0.00–3.00)		0.88 (0.88, 0.00–3.00)	
DAS28 score, mean (SD)	4.24 (1.52)	114 (4.9)	4.14 (1.52)	78 (4.7)
EQ-5D score, UK preference set		256 (11)		174 (10)
Mean (SD)	0.53 (0.33)		0.54 (0.33)	
Median (IQR, range)	0.66 (0.47, –0.59 to 1.00)		0.66 (0.47, –0.59 to 1.00)	
Previous no. sDMARD, mean (SD)	3.0 (1.9)	15 (0.6)	2.8 (1.8)	11 (0.7)
Previous no. bDMARD				
Naive	1831 (78)		1306 (78)	
1	371 (16)		263 (16)	
2	122 (5.2)		88 (5.3)	
3 or more	17 (0.7)		12 (0.7)	
Time since anti-TNF treatment start, mos				
Mean (SD)	15 (23)		14 (23)	
Median (IQR, range)	1.5 (24, 0–122)		1.5 (24, 0–122)	

IQR: interquartile range; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score; DMARD: disease-modifying antirheumatic drugs; sDMARD: synthetic DMARD; bDMARD: biologic DMARD; anti-TNF: antitumor necrosis factor.

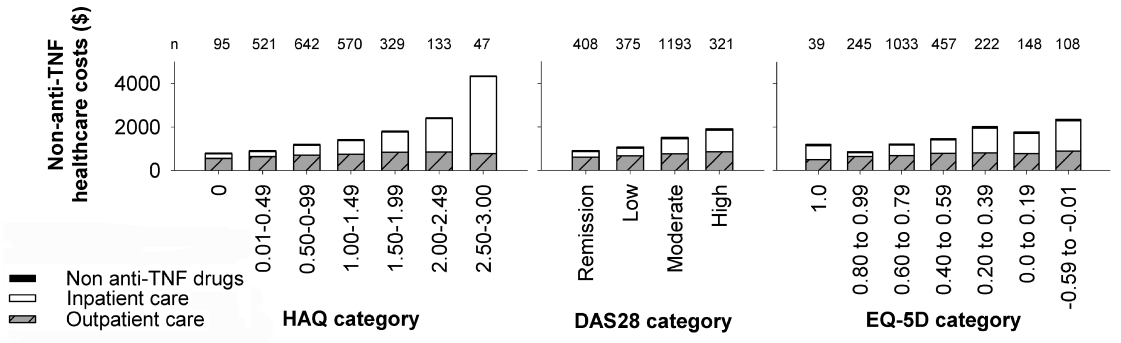

Figure 1. Mean non-anti-TNF healthcare cost distributions in the different categories of HAQ, DAS28, and EQ-5D scores (based on individual patient means). The number of patients in each category is given above the bars. Costs are in 2011 US dollars. anti-TNF: antitumor necrosis factor; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score.

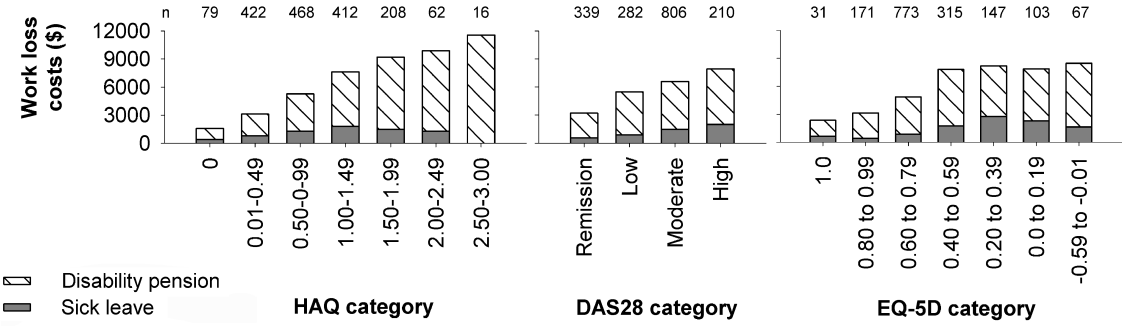

Figure 2. Mean work loss cost distributions in the different categories of HAQ, DAS28, and EQ-5D scores (based on individual patient means). The number of patients in each category is given above the bars. Costs are in 2011 US dollars. HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score.

work loss than non-anti-TNF healthcare costs ($p < 0.05$ for HAQ, DAS28, and EQ-5D; Table 2).

Healthcare costs. Comparing the 3 measures, HAQ correlated most closely to inpatient care while displaying the weakest association with non-anti-TNF drug costs. Overall, similar correlations with non-anti-TNF healthcare costs were observed for all measures.

Work loss costs. HAQ showed the strongest correlation to disability pensions and overall work loss costs. The association of EQ-5D to work loss costs was also superior to that of DAS28, although not reaching statistical significance regarding disability pensions alone ($p = 0.06$).

Societal costs. Non-anti-TNF societal costs correlated most closely to HAQ, followed by EQ-5D.

Regression analyses. Results of the regression analyses are presented in Table 3. Combining HAQ, DAS28, and/or

Table 2. Correlations of HAQ, DAS28, and EQ-5D scores to costs. Values are r (95% CI) unless otherwise specified.

Cost Category*	n	HAQ	DAS28	EQ-5D
Non-anti-TNF healthcare cost	2341	0.28 (0.24–0.32)	0.24 (0.20–0.28)	–0.25 (–0.21 to –0.29)
Non-anti-TNF drugs cost†#	2341	0.04 (–0.01 to 0.08)	0.15 (0.11–0.19)	–0.12 (–0.08 to –0.16)
Outpatient care cost	2341	0.19 (0.15–0.23)	0.20 (0.16–0.23)	–0.19 (–0.15 to –0.23)
Inpatient care cost†#	2341	0.26 (0.22–0.30)	0.14 (0.10–0.18)	–0.19 (–0.15 to –0.23)
Work loss cost†#‡	1669	0.51 (0.48–0.55)	0.31 (0.26–0.35)	–0.40 (–0.36 to –0.44)
Disability pension cost†#	1669	0.43 (0.39–0.47)	0.20 (0.15–0.24)	–0.26 (–0.21 to –0.30)
Non-anti-TNF societal cost†#‡	1669	0.54 (0.51–0.58)	0.35 (0.31–0.40)	–0.43 (–0.39 to –0.47)

* Missing data varied between 0.1% and 3.8%; sick leave is not presented separately since the absence of sick leave may be attributable to either good health or the presence of disability pension. † HAQ vs DAS28, $p < 0.05$. # HAQ vs EQ-5D, $p < 0.05$. ‡ DAS28 vs EQ-5D, $p < 0.05$. HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score; anti-TNF: antitumor necrosis factor.

EQ-5D scores as independent variables in the same linear models did not improve R^2 values by > 0.01 for any outcome.

Healthcare costs. Regardless of using individual means (linear models) or all observations (GEE models), HAQ scores were most closely related to non-anti-TNF healthcare costs, while no difference was detected between the associations of DAS28 and EQ-5D to this outcome.

Work loss costs. Disability pension status is an inert outcome, unlikely to change in response to temporal fluctuations of disease severity in the individual patient. The GEE models, by accounting for within-patient associations, thus resulted in substantially lower standardized β for work loss (and societal) costs for all 3 measures as compared with the models based on individual means. Nonetheless, by boot-strapped comparison of standardized β, both methods found a closer association of work loss costs to HAQ than to the other measures, while EQ-5D scores were also more strongly associated with this outcome than DAS28.

Societal costs. Non-anti-TNF societal costs were most closely related to HAQ by both methods. Using individual means, a stronger association of societal costs to EQ-5D than DAS28 was also observed, although this was not reproduced in the GEE analysis.

Unadjusted analyses. Results of the unadjusted analyses were similar to those of the adjusted (Figure 3; Supplementary Table 2 and Supplementary Figure 4, available online at jrheum.org).

DISCUSSION

Main findings. In RA, worse levels of HAQ disability, DAS28 disease activity, and EQ-5D HRQOL are all associated with increased non-anti-TNF healthcare and work loss costs. Apart from alleviating the burden of disease for the individual patient, interventions that avoid progression to worse disease states according to these measures may thereby also result in monetary savings for society. On the other hand, large variations of costs were seen across the full range of all the 3 measures, with correlations of 0.3 to 0.5 in regard to work loss, and even lower to healthcare costs. Other factors — RA-related or not — are thus also involved in the explanation of work disability and healthcare expenditures.

Of the studied measures, HAQ was consistently the best marker of non-anti-TNF societal costs. Both when comparing patients and when including within-patient transitions, a difference/change in HAQ reflected the corresponding difference in societal costs better than DAS28 or EQ-5D values, confirming the central role of functional deterioration as a driver of RA costs. In between-patient assessments, the superiority of HAQ was mainly explained by its closer relation to work loss costs, which accounted for > 80% of total non-anti-TNF costs in working-age patients. Because of the relative stability of disability pension status in the individual, all 3 measures, however, displayed substantially weaker relations to work loss costs when also accounting for within-patient associations. Nonetheless, the results remained in favor of HAQ. In non-anti-TNF healthcare costs, the observed between-measure differences were generally smaller than for work loss costs, although the regression models again revealed a statistically closer relation to HAQ than to DAS28 or EQ-5D. EQ-5D scores were also found to reflect work loss costs more closely than DAS28, whereas no difference was detected in relation to healthcare expenses.

Costs. A large number of RA cost-of-illness studies have been published. As reviewed elsewhere[33,34], comparison of cost results is inherently difficult because of the differences in healthcare systems, secular trends, and the large array of methodological approaches used. Further, our current study

Table 3. Associations of HAQ, DAS28, and EQ-5D scores to costs by linear and GEE regression.

Variables	Linear Regression Using Individual Patient Means*				GEE Regression Using all Visits*		
	Patients, n	Standardized β (95% CI)	p	R^2	Patients/Visits, n	Standardized β (95% CI)	p
Non-anti-TNF healthcare costs							
HAQ	2331	0.21 (0.15–0.27)†#	< 0.001	0.09	2331/13114	0.16 (0.13–0.19)†#	< 0.001
DAS28	2292	0.16 (0.11–0.21)	< 0.001	0.08	2292/12607	0.12 (0.10–0.14)	< 0.001
EQ-5D	2246	–0.15 (–0.21 to –0.10)	< 0.001	0.08	2246/11674	–0.11 (–0.14 to –0.09)	< 0.001
Work loss costs							
HAQ	1660	0.43 (0.39–0.48)†#	< 0.001	0.36	1660/8934	0.11 (0.07–0.15)†#	< 0.001
DAS28	1631	0.27 (0.23–0.32)	< 0.001	0.27	1631/8570	0.05 (0.03–0.06)	< 0.001
EQ-5D	1600	–0.34 (–0.38 to –0.29)‡	< 0.001	0.31	1600/7981	–0.07 (–0.08 to –0.05)‡	< 0.001
Non-anti-TNF societal costs							
HAQ	1660	0.46 (0.41–0.50)†#	< 0.001	0.38	1660/8934	0.21 (0.17–0.25)†#	< 0.001
DAS28	1631	0.30 (0.25–0.35)	< 0.001	0.28	1631/8570	0.11 (0.08–0.14)	< 0.001
EQ-5D	1600	–0.35 (–0.40 to –0.31)‡	< 0.001	0.32	1600/7981	–0.12 (–0.15 to –0.09)	< 0.001

* Adjusted for age, sex, disease duration, previous number of biologics used, time from start of the present anti-TNF therapy, and followup calendar year (applying individual patient means in the linear regression analyses and absolute values in the GGE regressions). † HAQ vs DAS28, $p < 0.05$. # HAQ vs EQ-5D, $p < 0.05$. ‡ DAS28 vs EQ-5D, $p < 0.05$ by bootstrapped comparison of standardized β. HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score; GEE: generalized estimating equations; anti-TNF: antitumor necrosis factor.

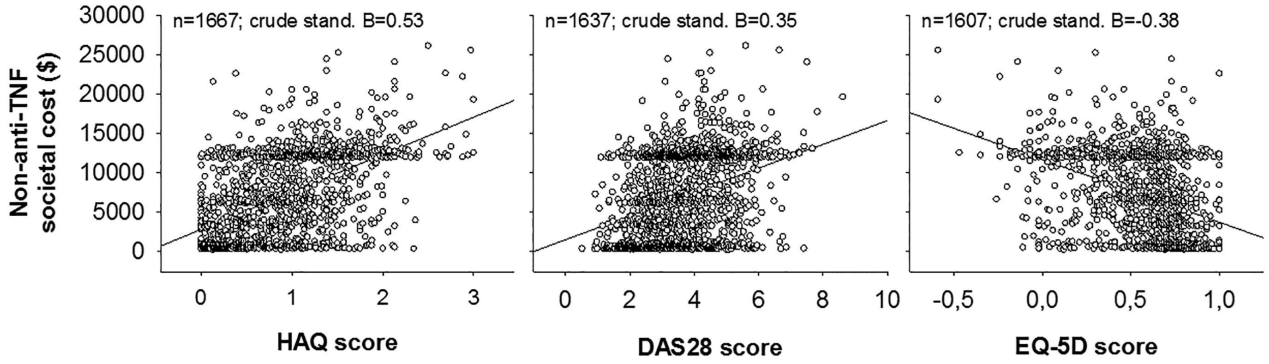

Figure 3. Scatterplots with fitted regression lines for HAQ, DAS28, and EQ-5D scores versus non-anti-TNF societal costs using individual patient means (between-patient assessment). Costs are in 2011 US dollars. anti-TNF: antitumor necrosis factor; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score.

was not designed primarily to describe costs, and deriving annual costs from our 60-day means (± 30 days around out-patient visits) may overestimate cost types typically exceeding the average in conjunction with a visit. Indeed, when restricting cost retrieval in our present analysis to the 30 days prior to each visit, mean daily outpatient care costs, as expected, decreased (by about 50%). The other cost types, however, remained fairly stable, indicating the overall risk of such overestimation to be limited. Moreover, this would not affect the main aim of the study: to compare how HAQ, DAS28, and EQ-5D relate to the various cost categories.

In comparison to a nationwide Swedish cost-of-illness study covering 2010[1], substantially higher annual non-anti-TNF societal costs are derived from our 60-day estimate. Apart from regional differences, this is mainly explained by shifting work loss patterns. While restricting our current analysis to visits during 2010 resulted in cost estimates similar to those of the nationwide study, considerably higher mean disability pension and in particular sick leave costs were seen during the early years of the study period, probably reflecting the stricter regulation of Swedish work loss compensations during later years, as well as a secular trend toward using anti-TNF therapy in less severely ill patients. In a wider comparison, the present healthcare cost estimate is in general agreement with earlier findings[5,10,33,35,36,37], whereas the work loss costs fall within the higher range of those previously reported[38], possibly reflecting the advanced disease in this group of anti-TNF–treated patients.

HAQ scores. HAQ is a well-established predictor of RA costs[34]. Several studies have shown mean healthcare and work loss costs to increase with rising HAQ levels by the same patterns as seen in Figure 1 and Figure 2[16,34,39], with some also reporting healthcare cost estimates similar to ours[37,40]. Deriving costs from a patient survey, a previous study from southern Sweden found correlations of HAQ to healthcare costs resembling our current results while reporting a lower association with work loss costs ($r_s = 0.33$)[5]. Others have, however, reported correlations of HAQ to work loss and total societal costs in line with ours[11,17]. A few previous studies have applied regression analysis to study the relationship between HAQ and costs, reporting R^2 values similar to ours at 0.06 and 0.45 in regard to healthcare and nonbiologics societal costs, respectively[11,16].

DAS28 scores. In comparison with HAQ, much less is known of how costs relate to DAS28. Two studies have reported mean nondrug healthcare costs to increase with rising DAS28 states, following a pattern resembling that of Figure 1[19,20], while both healthcare and work loss costs have also been found to rise with higher scores of the simplified disease activity index[41]. Further, elevated DAS28 in early disease has been shown to predict increased healthcare and work loss costs over the following years[18,42].

EQ-5D scores. As with HAQ, a previous study from southern Sweden found correlations of EQ-5D to healthcare costs similar to ours, while reporting a somewhat lower association with work loss costs ($r_s = –0.30$)[5]. Apart from this, however, very little is known.

Strengths and limitations. The large observational dataset encompassing > 13,000 visits in routine clinical practice is a major strength of our study. Further, by linkage to national registers, each visit could be coupled to objective cost data, resulting in a large sample of time-matched information on disease characteristics and costs while avoiding the bias of cost questionnaires.

We were unable to assess all societal cost components. Missing, for example, were primary care, community care and transportation, informal care, patients' out-of-pocket expenses, and loss of unpaid work or leisure time, which in a previous survey from southern Sweden (not including loss of unpaid work) amounted to 18% of nonbiologics societal costs[5]. Work loss costs for sick leave periods ≤ 14 days were also not included, although a study from the relevant region reported only 2% of sick leave episodes in RA to be this short[43]. Whether the inclusion of these cost types would have altered the relative associations with the studied measures remains unknown. Moreover, because we studied how HAQ,

DAS28, and EQ-5D scores relate to contemporary (± 30 days around outpatient visits) rather than future costs, whether any of these measures predict costs beyond 30 days cannot be discerned from our current results. Because of the difficulties of assigning costs specifically to RA or other causes[44], all patient care and work loss costs were included, while drug costs were, however, limited to antirheumatic prescriptions. As implied by the relatively small R^2 values in Table 3, especially in relation to healthcare costs, other factors such as comorbidity status are likely to explain part of the variations in costs. Whether adjustment for comorbidities in the regression analyses would have altered the relative associations of the 3 measures to costs also remains unknown. On the other hand, in the daily meetings with patients in the clinic, we believe it to be of greater interest to rheumatologists to know how these commonly used measures reflect overall costs, regardless of comorbidity status.

While we believe our overall findings to be generalizable, the cost estimates may not be directly transferable to non-Swedish settings. For this reason, the numerical distributions of outpatient visits (differentiating between rheumatologist and other specialist visits), inpatient, and work loss days across the HAQ, DAS28, and EQ-5D categories are also presented in Supplementary Figure 5 (available online at jrheum.org). Likewise, the median disease duration of 10 years and the restriction to anti-TNF–treated patients may compromise generalizability to subjects with early disease or to the RA population at large. On the other hand, patients requiring biologic therapy also generate the highest nonbiologics costs to society[1], rendering them particularly important to study.

HAQ disability, DAS28 disease activity, and EQ-5D HRQOL are all associated with non-anti-TNF healthcare and work loss costs in established RA. HAQ was found to reflect both cost types more closely than the other measures, although the differences were less pronounced in regards to healthcare costs. Despite this, the HAQ model only explained 38% of between-patient variations in non-anti-TNF societal costs, while the relation was even weaker when accounting for within-patient associations, a finding with potential implications for health economic modeling studies assigning costs indirectly based on HAQ transitions. Nonetheless, avoiding disease progression to stages with advanced disability would offer large potential savings to society.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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