The association of fatigue, comorbidity burden, disease activity, disability and gross domestic product in patients with rheumatoid arthritis. Results from 34 countries participating in the Quest-RA programme

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Abstract

Objective

The aim is to assess the prevalence of comorbidities and to further analyse to which degree fatigue can be explained by comorbidity burden, disease activity, disability and gross domestic product (GDP) in patients with rheumatoid arthritis (RA).

Methods

Nine thousands eight hundred seventy-four patients from 34 countries, 16 with high GDP (>24.000 US dollars [USD] per capita) and 18 low-GDP countries (<24.000 USD) participated in the Quantitative Standard monitoring of Patients with RA (QUEST-RA) study. The prevalence of 31 comorbid conditions, fatigue (0–10 cm visual analogue scale [VAS] [10=worst]), disease activity in 28 joints (DAS28), and physical disability (Health Assessment Questionnaire score [HAQ]) were assessed. Univariate and multivariate linear regression analyses were performed to assess the association between fatigue and comorbidities, disease activity, disability and GDP.

Results

Overall, patients reported a median of 2 comorbid conditions of which hypertension (31.5%), osteoporosis (17.6%), osteoarthritis (15.5%) and hyperlipidaemia (14.2%) were the most prevalent. The majority of comorbidities were more common in high-GDP countries. The median fatigue score was 4.4 (4.8 in low-GDP countries and 3.8 in high-GDP countries, p<0.001). In low-GDP countries 25.4% of the patients had a high level of fatigue (>6.6) compared with 23.0% in high-GDP countries (p<0.001). In univariate analysis, fatigue increased with increasing number of comorbidities, disease activity and disability in both high- and low-GDP countries. In multivariate analysis of all countries, these 3 variables explained 29.4% of the variability, whereas GDP was not significant.

Conclusion

Fatigue is a widespread problem associated with high comorbidity burden, disease activity and disability regardless of GDP.

Key words

QUEST-RA, rheumatoid arthritis, fatigue, comorbidity, disease activity

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Introduction

Rheumatoid arthritis (RA) presents with a multitude of symptoms and challenges for patients and physicians. Unlike normal tiredness, fatigue is chronic, typically not related to overexertion and poorly relieved by rest (1). Persistent fatigue is a major problem for many patients with RA, and fatigue is as severe and frequent as pain (2). Little attention has been paid to its multidimensional nature and its wide-ranging consequences for the patients (3). However, in 2006 the Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommended to include fatigue in the core set of outcome measures for clinical trials (4), thus emphasising its importance. Despite the increasing focus on fatigue, its association with different aspects of the disease (*e.g.* inflammation, disability, comorbidities) remains poorly understood.

Comorbid medical conditions are common in patients with RA. Some comorbidities are causally associated with RA, while others are related to its treatment (5). Irrespectively of their underlying pathogenesis, comorbidities increase disability (6) and shorten life expectancy (7). It is unknown how the comorbid burden is distributed in countries with different economic status, and knowledge on the association between comorbidity burden and fatigue is limited.

RA is characterised by inflammation, disability and joint destruction. Studies suggest that disease activity and disability contribute significantly to fatigue (8). Studies on the association between fatigue and disease activity, functional status and comorbidities, are, however few (9), and it is unknown whether such associations vary across different RA populations.

The Quantitative Standard monitoring of Patients with RA (QUEST-RA) study is an international collaborative effort to investigate RA in many countries. Previous results from the QUEST-RA study showed that Gross Domestic Product (GDP), which is considered an indicator of a country's standard of living, is strongly inversely associated with disease activity (10, 11).

We analysed QUEST-RA data to study the comorbid burden across 34 countries and associations between fatigue, comorbidities and disease burden in patients with RA and the GDP of their resident country.

Materials and methods

Study population

The QUEST-RA programme was established in 2005 to promote quantitative assessment in usual care at multiple sites and developing a database of RA patients seen in regular care in several countries. One hundred consecutive non-selected patients at ≥3 sites per country were enrolled (12). By January 2012 the programme included 9,874 patients from 104 sites in 34 countries (Table I). Each included patient was assessed by the SPERA protocol, a standard protocol to evaluate RA, consisting of a four-page patient self-report questionnaire and a three-page clinician assessment. Details of the SPERA protocol and QUEST-RA have been published previously (12, 13).

Ethics committee approvals

The study was conducted according to the Declaration of Helsinki. Approval for the study was obtained from local Internal Review Boards or Ethics Committees according to local requirements.

Study variables

Fatigue, pain and patient's global assessment of disease activity (PTGL) were scored on a 10 cm visual analogue scale (VAS). The phrasing of the fatigue VAS was: "How much of a problem has UNUSUAL fatigue or tiredness been for you OVER THE PAST WEEK?" with the anchors "Fatigue is no problem: 0" and "Fatigue is a major problem: 100". The highest tertile (>6.6) was chosen arbitrarily to indicate high level of fatigue. The physician completed information concerning 31 comorbidities by interview of patients and review of patients' files (Table II). Body weight and height were obtained from the patient, and body mass index (BMI) was calculated. Obesity was defined as body mass index (BMI) greater than 30 kg/m^2.

RA disease activity was measured by Disease Activity Score based on assessment of 28 joints (DAS28). DAS28

was calculated with 3 variables: number of tender (TJC) and swollen (SJC) joints on examination of 28 joints, and erythrocyte sedimentation rate (ESR). We used DAS28 without the PTGL because of the latter's high collinearity with the fatigue score.

Disability was assessed by the health assessment questionnaire (HAQ) (14).

Standard of living in each country was estimated by the GDP in year 2011 (15) and expressed in US dollars (USD) per capita. Sixteen countries with a GDP per capita equal to or greater than 24.000 USD were classified as "high-GDP" (Canada, Denmark, England, France, Finland, Germany, Greece, Ireland, Italy, Japan, the Netherlands, Norway, Spain Sweden, United Arab Emirates, USA), and 18 countries with a GDP per capita less than 24.000 were classified as "low-GDP" (Argentina, Brazil, Egypt, Estonia, Hungary, India, Kenya, Kosovo, Latvia, Lithuania, Morocco, Poland, Romania, Russia, Serbia, South Korea, Taiwan, Turkey) (10).

Statistical methods

Descriptive results are presented as mean with standard deviation (SD) in parentheses, median with Inter Quartile Range (IQR) in parentheses or as percentages. Comparisons between groups were performed using Mann-Whitney U-test for non-parametric continuous variables, *t*-test for parametric continuous variables and Chi-square test for categorical variables. Analyses were two-sided with a significance level of 0.05.

To identify relevant variables for the multivariate analyses, univariate regression analyses with fatigue score as the dependent variable were performed. The following variables were tested: number of comorbidities (0–31), DAS28, HAQ, pain and PTGL. Significant variables were included in a linear multiple regression analysis with backward selection adjusted for age and gender to identify demographic and clinical measures independently associated with fatigue. We chose not to include pain and PTGL in the multiple regression analysis, because both variables have been reported to correlate closely with fatigue. In our dataset Spearman's rho was 0.596 ($p<0.05$) for pain and 0.557 ($p<0.05$) for PTGL. Multiple regression analyses were performed in three groups: the total QUEST-RA population, low-GDP countries and high-GDP countries.

Results

Patients

As of January 1st 2012 the QUEST-RA database included 9,874 patients from 104 sites in 34 countries. The mean age was 54.9 years, 75.8% were woman, and the median disease duration was 8.1 years (Table I). Compared with patients in high-GDP countries, patients in low-GDP countries were younger (52.4 *vs.* 57.8 years), more were women (76.9% *vs.* 74.6%), with shorter disease duration (7.9 *vs.* 8.7 years), and fewer were Caucasians (52.7% *vs.* 83.6%), Table I.

Fatigue

Overall, the median fatigue score was 4.4, with average score higher in the low-GDP compared to high-GDP countries (4.8 *vs.* 3.8, $p<0.001$). In low-GDP countries 25.4% of the patients had a high level of fatigue (>6.6) compared with 23.0% in high-GDP ($p<0.001$). In the total population 24.4% had a fatigue score >6.6.

Comorbidities

For the distribution of comorbidities see Table II. The most frequent comorbid conditions were hypertension (31.5%), osteoporosis (17.6%), osteoarthritis (15.5%), hyperlipidaemia (14.2%), obesity (14.1%), chronic back pain (13.4%), thyroid disease (10.4%) and peptic ulcer disease (8.5%) (Table II).

Overall, patients had a median of 2 comorbid conditions and 25.8% had zero comorbidities, 23.1% had 1 comorbidity, 17.9% had 2 comorbidities, 12.6% had 3 comorbidities, 8.0% had 4 comorbidities, 5.2% had 5 comorbidities and 7.4% had between 6 and 17 comorbidities.

In high-GDP countries, patients had a median of 2 comorbidities, while patients in low-GDP had 1. Eleven of the comorbidities (angina, coronary artery disease, peptic ulcer, inflammatory bowel disease, impaired renal function, chronic bronchitis, Parkinson's disease, osteoarthritis, psychiatric disease, AIDS, alcoholism and obesity) were evenly distributed in high- and low-GDP countries. All other comorbidities (17) were more common in high-GDP countries except for chronic back pain, osteoporosis and hypertension, which were more common in the low-GDP countries (Table II).

Disease activity

Patients in low-GDP countries had significantly higher disease activity by both physician-derived measures and patient self-reported scores, in comparison with patients in high-GDP countries (Table I). In high-GDP countries 41.7% of the patients had low disease activity (DAS28<3.2) while only 19.6% of the patients in the low-GDP countries ($p<0.001$) had low disease activity. A total of 16.9% in high-GDP countries fell in the category of a high DAS28 score (>5.1) compared with 40.2% in low-GDP countries ($p<0.001$).

Physical function

Overall, patients had a median HAQ score of 0.88. Patients in high-GDP countries scored lower (0.75) compared with patients in low-GDP countries (1.00) (Table I). In high-GDP countries 60.0% of the patients had a HAQ score between 0 and 1. In low-GDP countries it was 46.9% of the patients ($p<0.001$). A HAQ score between 2 and 3 was found in 7.4% of high-GDP patients and in 12.9% of low-GDP patients ($p<0.001$).

Fatigue versus comorbidities, disease activity and physical function

Fatigue score increased with increasing number of comorbidities in both high- and low-GDP countries (Fig. 1A). However, patients from low-GDP countries reported more fatigue regardless of the comorbid burden (all *p*-values<0.05 except for comorbidities=3 and 4, Fig. 1A). In high-GDP countries the median fatigue score increased from 2.8 in patients with no comorbidities to 5.3 in patients with ≥5 comorbidities. In low-GDP countries fatigue score increased from 4 to 6.2. When fatigue was replaced by other patient self-reported variables (*i.e.* pain and PTGL), a similar pattern was observed. In patients with little pain (<3.33 the lowest tertile), the fatigue score was 2.73.

Table I. Characteristics of the study population in high and low GDP countries in the QUEST-RA.

	Total	High-GDP	Low-GDP	*p*-value (high *vs*. low GDP)
Number of patients with available data	7683–9715	3630–4388	4053–5327	
Patient characteristics				
Age in years, mean (SD)	54.9 (13.8)	57.8 (13.7)	52.4 (13.4)	<0.031[3]
Women, %	75.8	74.6	76.9	<0.030[1]
Disease duration in years	8.1 (3.7–15.0)	8.7 (3.8–16.1)	7.9 (3.6–14.1)	<0.001[2]
RF positve, %	73.2	71.4	74.7	<0.001[1]
Erosive disease, %	54.0	52.2	55.4	<0.001[1]
Race,caucasian, %	63.8	83.6	52.7	<0.001[1]
Number of comorbidities (0-31)	2 (0–3)	2 (1–3)	1 (0–3)	<0.001[2]
Disease activity measures				
DAS28_3, mean (SD)	4.2 (1.58)	3.6 (1.43)	4.7 (1.55)	<0.001[3]
ESR	24 (12–42)	18 (10–34)	30 (16–48)	<0.001[2]
SJC (0 to 28)	2 (0–6)	2 (0–5)	3 (0–8)	<0.001[2]
TJC (0 to 28)	4 (1–11)	2 (0–6)	7 (2–14)	<0.001[2]
Physician global (0 to 10)	2.6 (1–4.9)	1.7 (0.5–3.5)	3.5 (1.6–5.6)	<0.001[2]
Patient self-report				
HAQ physical function (0 to 3=worst)	0.88 (0.25–1.50)	0.75 (0.25–1.25)	1 (0.37–1.62)	<0.001[2]
Pain VAS (0 to 10)	4 (1.7–6.1)	3.2 (1.2–5.8)	4.5 (2.1–6.5)	<0.001[2]
Patient global VAS (0 to 10=worst)	4.1 (1.9–5.9)	3.2 (1.3–5.4)	4.7 (2.5–6.4)	<0.001[2]
Fatigue VAS (0 to 10=worst)	4.4 (1.8–6.8)	3.8 (1.4–6)	4.8 (2.2–7)	<0.001[2]

[1]: Chi-squared test; [2]: Mann-Whitney U-Test; [3]: *t*-test. Variables are median (IQR) unless otherwise mentioned.
DAS28_3: Disease activity score in 28 joints (based on 3 variables); ESR: erythrocyte sedimentation rate; GDP: gross domestic product; HAQ: health assessment questionnaire; IQR: interquartile range; Physician global: physician global estimate of status; RF: rheumatoid factor; SJC: swollen joint count; SD: standard deviation; TJC: tender joint count; VAS: visual analogue scale.

Table II. Distribution of comorbidities in low- and high-GDP countries in the QUEST-RA.

Comorbidities	Total %	High-GDP %	Low-GDP %	*p*-value* (high *vs*. low-GDP countries)
Hypertension	31.5	29.7	32.8	<0.001
Angina	4.4	4.0	4.7	0.058
Heart attack	2.5	3.6	1.6	<0.001
Coronary artery disease	4.6	4.8	4.4	0.436
Other heart disease	4.8	5.8	3.9	<0.001
Hyperlipidaemia	14.2	16	12.7	<0.001
Peripheral vascular disease	2.9	3.6	2.4	<0.001
Peptic ulcer disease	8.5	8.6	8.6	0.724
Inflammatory bowel disease	1.2	1.3	1.1	0.226
Impaired renal function	2.6	2.6	2.6	0.876
Asthma	4.5	6.4	3	<0.001
Chronic bronchitis	4.0	4.3	3.8	0.272
Diabetes mellitus	7.5	8.9	6.9	0.008
Thyroid disease	10.4	11.4	9.6	0.008
Cancer	3.4	6.1	1.9	<0.001
Stroke	1.4	2.0	0.9	<0.001
Parkinson's disease	0.4	0.3	0.4	0.808
Chronic back pain	13.4	12.3	14.3	0.002
Musculoskeletal trauma	4.5	5.8	3.5	<0.001
Low energy fractures	4.5	5.1	4.0	0.012
Osteoporosis at scan	17.6	16.6	18.4	0.008
Osteoarthritis	15.5	15.7	15.3	0.856
Infection requiring hospitalisation	6.3	7.6	5.3	<0.001
Herpes zoster/Shingles	3.8	5.3	2.5	<0.001
Fibromyalgia	3.4	3.8	3.0	0.033
Psoriasis	1.9	3.2	0.8	<0.001
Cataracts	6.8	7.8	6.0	<0.001
Psychiatric disease	4.5	5.8	3.5	<0.001
AIDS	0.1	0.0	0.1	0.824
Alcoholism	0.6	0.7	0.5	0.191
Obesity (BMI>30 kg/m^2)	14.1	15.3	13.2	0.128

*Mann-Whitney U-test.

With increasing disease activity, fatigue score was higher, and there was no difference in fatigue score between patients from high and low GDP countries with similar disease activity. Thus, the median fatigue score was 2.2 in patients with DAS28≤3.2 and 5.8 in patients with DAS28≥5.2, (Fig. 1B). Fatigue score increased with increasing disability (Fig. 1C). There was significant difference in fatigue score between high- and low-GDP countries in the group of patients with low HAQ score (<1), but not in the groups with intermediate (1–1.99) and high (≥2) HAQ scores. In high-GDP countries the median fatigue score increased from 2.3 (HAQ score <1) to 7.2 (HAQ score >2). The pattern was the same in low-GDP countries, except the median fatigue score in the lowest HAQ-group was 2.9. In Figure 2, fatigue score was plotted against GDP per capita in each of the participating countries, and showed a strong negative correlation (Persons correlation coefficient=-0.539).

Regression analyses

All variables tested (number of comorbidities, DAS28, HAQ, pain, patient global, age and gender) were statistically significant in the univariate anal-

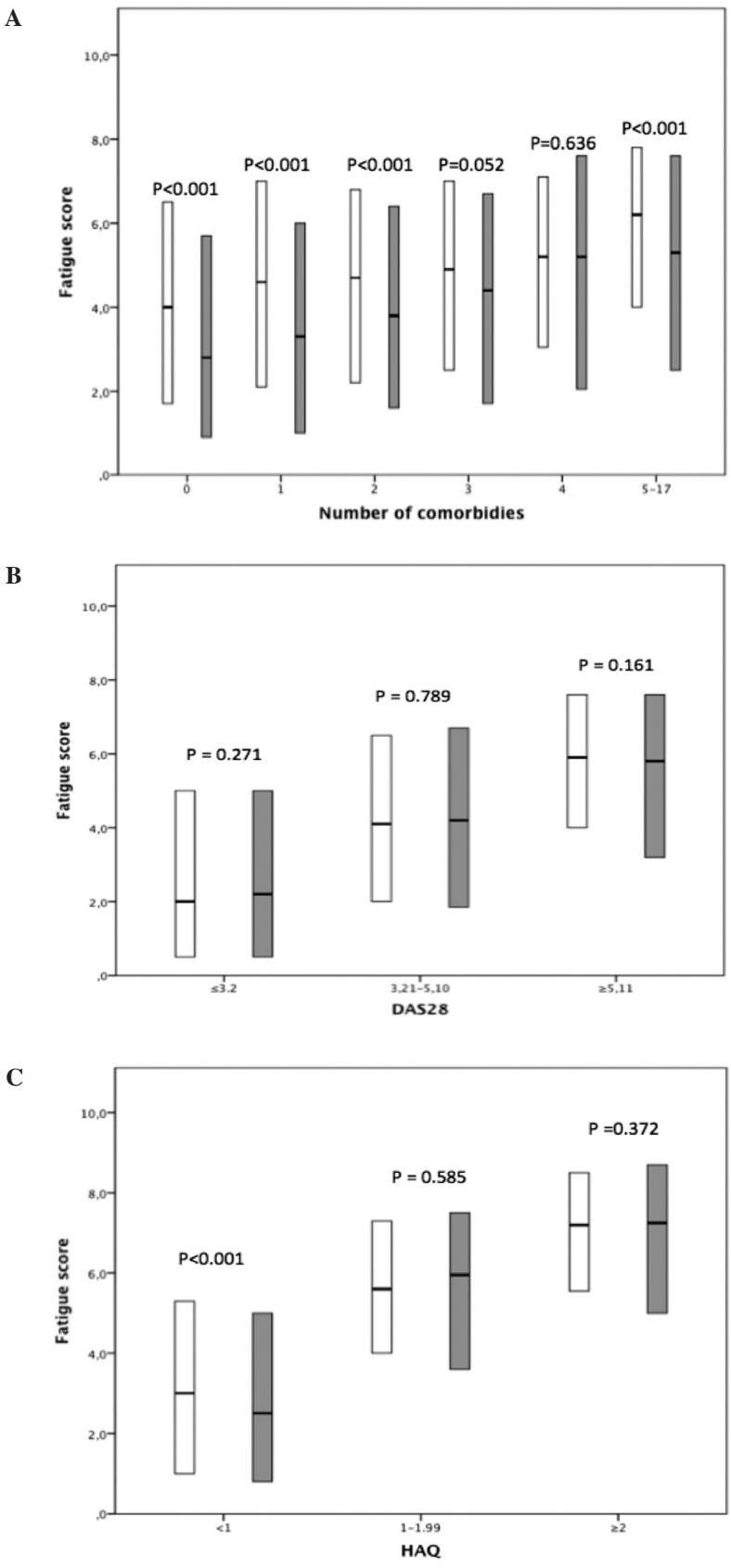

Fig. 1. Fatigue and its association with **A**: comorbidities, **B**: disease activity and **C**: disability, respectively. Grey bars: high-GDP countries. White columns: low-GDP countries. DAS28_3: disease activity score of 28 joints. HAQ: Health Assessment Questionnaire. Shown are medians and interquartile ranges. Mann-Whitney U-test.

yses with fatigue level as the dependent variable (Table III).

In the multiple regression analysis for the total QUEST-RA cohort with fatigue as the dependent variable, comorbidities (0 to 31), DAS28 and HAQ, but not GDP, were statistically significant explanatory variables after adjustment for age and gender (Table III). Together, these 3 variables explained 29.4% of the variability.

For high-GDP countries, comorbidities, DAS28 and HAQ were independent explanatory variables for fatigue and explained 29.5% of variability in fatigue. In low-GDP countries fatigue was associated with HAQ and DAS28, but not with comorbidity burden, and the two variables together had an R^2 value of 0.284 (Table III).

Discussion

The main finding in this large, multinational study was that fatigue remains a major problem for RA patients in all countries with one in four patients scoring high on fatigue. Overall, increased comorbidity burden, disease activity and disability were independently associated with increased fatigue regardless of the standard of living as expressed by GDP per capita. Patients in low-GDP countries suffered more fatigue, which was explained by higher disease activity and HAQ.

The most common comorbidities were related to cardiovascular disease with hypertension affecting one in three patients and hyperlipidaemia one in six and diabetes affecting 7%. Osteoporosis with or without fracture had been diagnosed in more than 15% of patients and overall 14.1% of patients were obese with a BMI >30 kg/m^2. About 10% reported to be suffering from thyroid diseases. Peptic ulcer disease was also a common complication, and chronic back pain and osteoarthritis were prevalent conditions (13–15%). A previous study from Spain including 277 patients reported similar results for hypertension (27%) and thyroid-disease (13%), but a higher prevalence for obesity (26%), and also respiratory (12%) and upper gastrointestinal disorders (10%) were prevalent(16). Chung *et al*. reported hypertension in 57% of

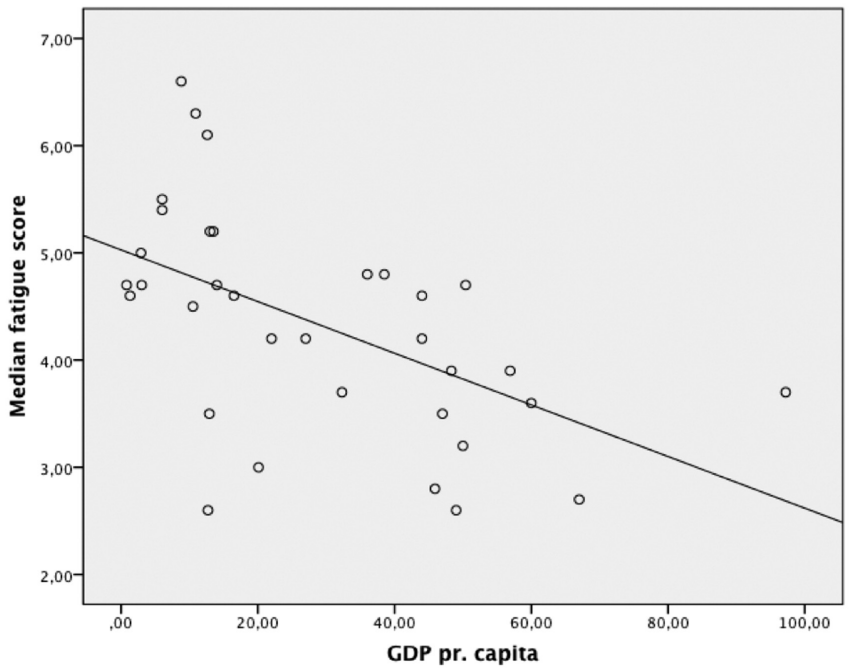

Fig. 2. Association between gross domestic product per capita in year 2011 (GDP) and fatigue score in 34 countries in the QUEST-RA study. Persons correlation coefficient=-0.539, and R^2=0.291.

197 patients from the US compared to 42% in 274 control subjects (17). Hypertension was diagnosed in 70.5% in a study from the United Kingdom (18). Of the patients with hypertension 61% received anti-hypertensive treatment, whereas 39% was previously undiagnosed (18). In both studies a careful, protocolled measurement of blood-pressure was performed in each patient (17). This is in contrast to our data, which were based on interviewing the patients and examining patient files. The prevalence of osteoporosis was similar in a study of 394 female RA patients in Oslo, in which an overall frequency of 14.7% in femoral neck and total hip and 16.8% in the spine was reported. This was a two-fold higher prevalence of osteoporosis compared with that in the general population (19). We were surprised that patients in high-GDP countries reported more comorbidities than patients in low-GDP countries. Since the registration was based on interviews, we were not able to validate the findings, and we have no information regarding the severity of the comorbidities. It is, however, likely that comorbidities are under-diagnosed and probably less effectively treated in poorer countries. Currently, only few studies of comorbidities in patients with RA in low-GDP countries have been conducted. The Brazilian Society of Rheumatology (SBR) recently published a paper aiming at developing recommendations for the diagnosis and management of comorbidities in patients with RA (20). They focused on what they expected to be the most common and severe comorbidities: hypertension, diabetes mellitus, dyslipidemia, atherosclerosis, metabolic syndrome, venous thrombosis and pulmonary embolism, malignancies and osteoporosis. No prevalence has been reported so far. This project reflects an important, initial focus on the comorbid burden in RA patients in low-GDP countries. Two studies from India focused on subclinical atherosclerosis (21, 22). In the first study, 19 of 57 RA patients (33.3%) and 2 of 45 controls (4.44%) had abnormal carotid intima-media thickness (validated surrogate marker of atherosclerosis) measured by ultrasound (21). In the second study, including 35 early RA patients and 35 healthy controls, the carotid intima-media thickness was significantly higher in RA patients than in controls (22), which suggests that patients with early RA have premature atherosclerosis. One may hypothesise

Table III. Uni- and multi-variate linear regression analyses adjusted for age and gender to identify factors contributing to fatigue in the QUEST-RA study in 34 countries with high (>24.000 USD per capita) or low GDP (<24.000 USD).

	Univariate						Multivariate					
	Total population coefficients	*p*-value	High-GDP countries coefficients	*p*-value	Low-GDP countries coefficients	*p*-value	Total population coefficients	*p*-value	High-GDP countries coefficients	*p*-value	Low-GDP countries coefficients	*p*-value
Comorbidities 0–31	0.241 (0.212–0.270)	<0.001	0.279 (0.238–0.321)	<0.001	0.234 (0.187–0.269)	<0.001	0.101 (0.072–0.131)	<0.001	0.177 (0.135–0.218)	<0.001	–	–
DAS28_3	0.697 (0.660–0.734)	<0.001	0.677 (0.617–0.738)	<0.001	0.727 (0.677–0.776)	<0.001	0.247 (0.205–0.290)	<0.001	0.224 (0.158–0.290)	<0.001	0.290 (0.231–0.348)	<0.001
HAQ	1.938 (1.873–2.004)	<0.001	2.054 (1.950–2.157)	<0.001	1.830 (1.744–1.915)	<0.001	1.632 (1.543–1.720)	<0.001	1.806 (1.672–1.940)	<0.001	1.536 (1.422–1.650)	<0.001

Coefficients (95% confidence intervals) are presented. DAS28_3: disease activity score in 28 joints (based on 3 variables), HAQ: health assessment questionnaire; GDP: gross domestic product; QUEST-RA: quantitative Standard monitoring of patients with rheumatoid arthritis; USD: US dollars. N and R^2 were 7,414 and 0.294 in the total population, respectively. For high-GDP countries, they were 3,407 and 0.295, and for low GDP-countries 4,411 and 0.285, respectively.

that under-diagnosing comorbidities in low-GDP countries may, at least in part, explain why fatigue was only independently associated with the number of comorbidities in high-GDP countries. The comorbidities may also be more severe in low-GDP countries due to limited treatment resources. In contrast, DAS28 and HAQ were positively associated with fatigue in all regression analyses irrespectively of GDP status.

The inflammatory activity of RA is reflected in the DAS28 score. We found the DAS28 score to be inversely associated with GDP. This was consistent with previous findings on a smaller sample size (10). In the present study there was a negative correlation between fatigue and GDP. In the multivariate analysis the high level of fatigue in low-GDP countries seemed to be explained by higher disease activity level. This supports the hypothesis that inflammation is a significant source of fatigue in RA.

Two studies from the nineties reported that fatigue is associated with disability (2, 23), and the present study demonstrated that this is still the case in today's RA patients. Thus we found a doubling in fatigue score from 2.3 (high-GDP) and 2.9 (low-GDP) to 7.2 between patients with the lowest HAQ score (<1) and patients with the highest HAQ score (>2). Our findings are supported by a Dutch study, which reported that patients with severe fatigue scored on average 0.6 units higher on HAQ, compared to patients without severe fatigue (24). In 557 patients from a hospital in the United Kingdom, fatigue was associated with DAS28, HAQ and pain. Correlation with fatigue was strongest for HAQ, and together the 3 variables explained 54% of the variance in fatigue score (25). They did not investigate how comorbidities were related to fatigue. In the present study, we found that fatigue was a significant problem also in patients with little pain. In our model comorbidities (0–31), DAS28 and HAQ explained 30% of the variance in fatigue, which means that 70% of the variation in fatigue was caused by other factors including, *e.g.,* pain and psychosocial factors.

RA patients rate fatigue as a very important aspect of the disease (4, 26). No internationally accepted definition of how to assess fatigue has been established (27). In the present study, fatigue was scored by the patients on a 10 cm visual analogue scale.

It is generally accepted that fatigue is a complex symptom and remains an enigma (28). It is caused by interaction of clinical factors and psychosocial issues (29), which has far-reaching consequences (30, 31). Hewlett *et al*. have proposed a conceptual model for RA fatigue (32), suggesting interactions between three factors: 1) disease processes (RA), 2) thoughts, feelings and behaviours, and 3) personal life issues including health issues such as comorbidities. In this study we confirmed the influence of disease processes (expressed as DAS28 and HAQ) on fatigue, but also demonstrated that comorbidities contribute to the fatigue burden in high-GDP countries. It remains unknown how psychosocial parameters, cultural and economic factors impact on RA patients' experience of fatigue.

This study has several limitations. First, it is possible that more RA patients with poor clinical status visit clinics in countries with lower GDP, and patients with better status in richer countries have a lower threshold to seek medical care and better treatment may be available in high GDP countries. Also the comorbidities were partly self-reported and may not be accurate. Secondly, we lack an objective marker of fatigue. We used the uni-dimensional VAS fatigue. Hewlett *et al*. have validated 23 different scales that have been used to measure RA fatigue. Seventeen scales had limited or no data on validation in RA. The VAS fatigue was one of only six scales, which were found to be reasonably valid and sensitive to change (27).

Conclusion

In conclusion, fatigue remains a widespread problem for RA patients. Fatigue score increases with increasing comorbidity burden, disease activity, and disability regardless of GDP. Patients in low-GDP countries suffered more fatigue, which was partially explained by higher disease activity. The percentage of patients with comorbidities was overall higher in high-GDP countries, but comorbidities might be under-diagnosed especially in low-GDP countries. The results of this study support the importance of improving the clinical status of patients with RA in all countries, which may in turn have a significant impact on and improve fatigue status in this patient group. Further other factors that contribute to fatigue need to be studied to improve overall quality of life of patients with RA.

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