A comparison of fatigue correlates in rheumatoid arthritis and osteoarthritis: disparity in associations with disability, anxiety and sleep disturbance

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Abstract

Objectives. To investigate correlates of fatigue among individuals with RA and OA, including mood, sleep, disease activity and radiographic damage.

Methods. Fatigue was assessed using the Multidimensional Assessment of Fatigue-Global Fatigue Index (MAF-GFI) in 103 patients with RA and 103 with OA. Sleep disturbance and pain were assessed using a visual analogue scale anxiety and depression using the Hospital Anxiety and Depression scale and disability using the HAQ. In the RA cohort, the disease activity score-28 joint count (DAS-28) and the Van der Heijde modified Sharp score were calculated, and in the OA cohort, the Kellgren–Lawrence score and the WOMAC score calculated.

Results. The MAF-GFI scores were higher in the OA cohort ($P = 0.02$). This was not significant after controlling for disability ($P = 0.59$). OA participants reported greater pain, disability, depression and sleeplessness than those with RA (all $P < 0.01$). The strongest correlates of fatigue in the RA cohort were depression ($P < 0.001$) and anxiety ($P < 0.001$). There was no significant association with pain ($P = 0.43$), DAS-28 ($P = 0.07$), HAQ ($P = 0.10$) or Sharp score ($P = 0.78$). In OA, the correlates of fatigue were older age ($P = 0.02$), sleep disturbance ($P = 0.03$), depression ($P = 0.04$), disability ($P = 0.04$) and lower CRP ($P = 0.001$).

Conclusions. Fatigue is common and severe in both RA and OA. In RA, fatigue had no significant association with pain, disease activity, disability or erosions, but was associated with depression and anxiety. The disparity in correlates indicates that generalizing the experience of fatigue between OA and RA is not appropriate. Fatigue is an important domain in the assessment of disease impact.

Key words: Rheumatoid arthritis, Osteoarthritis, Multidimensional assessment of fatigue, Depression, Disease activity.

Introduction

Fatigue is frequently identified as a significant symptom by people with many rheumatic diseases, including RA and OA [1, 2]. In qualitative studies, people with RA distinguish between systemic fatigue, related to their arthritis and general tiredness [3]. Patients with RA describe not only physical fatigue, but also cognitive fatigue, which manifests as a lack of motivation, an inability to think clearly or to concentrate [4, 5]. The reported prevalence of fatigue in RA varies widely depending on the criteria used, but the prevalence of clinically relevant fatigue is commonly given as between 40 and 80% [6–9], with 40% experiencing persistent severe fatigue [10]. Although there is no agreed definition of fatigue in RA, qualitative studies suggest that there are cognitive and emotional elements above and beyond physiological muscle fatigue [2, 3], a funding supported by psychometric studies utilizing specific questionnaire measures [1, 6]. The importance of fatigue has been demonstrated by the

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observation that fatigue is one of the commonest reasons for patients with RA to leave the workforce [11]. As a result of the above evidence, it was proposed at the Eighth OMERACT Conference that fatigue be considered for inclusion in the OMERACT core data set for RA studies [12].

The mechanisms by which the experience of fatigue arises are not clearly understood, but a number of correlates have been identified that appear to influence the severity of fatigue in RA. These include pain [6, 7, 9, 13, 14], functional status [6, 7, 9, 13, 14], sleep quality [6, 7, 9, 13, 14], depression [6, 7, 9, 13, 14], self-efficacy [6, 7, 9, 13–15], and illness perceptions [16]. Fatigue is also a prevalent symptom in OA, although this relationship has been studied less extensively [6, 17, 18]. In one study, a similar prevalence of substantial fatigue was noted in both RA and OA (41%) [6].

Fatigue is a subjective experience and its assessment has been the focus of considerable interest in recent years. Several different instruments have been developed to assess fatigue in a variety of different chronic conditions, including chronic fatigue syndrome [2, 4] and multiple sclerosis [19]. In individuals with RA, the Multidimensional Assessment of Fatigue—Global Fatigue Index (MAF-GFI), Short Form 36 (SF-36) vitality scale and a variety of visual analogue scales (VASs) have been studied in most detail [20–22]. The perception of fatigue may differ between RA and other conditions and therefore generic scales like the SF-36 may be unreliable or difficult to interpret. In a systematic review of scales used to assess fatigue in studies of RA, 23 scales were identified, of which 17 had limited or no data on validation in RA [20]. Some scales such as the Multidimensional Fatigue Inventory (MFI) [19] may be unsuitable for use in RA as they may not adequately discriminate between the overlapping elements of disability and fatigue. The validity of the widely used SF-36 vitality scale as a surrogate for fatigue has been questioned [20]. VAS fatigue scales have been widely used but poorly defined in terms of descriptors and qualifiers [20]. Only seven scales have evidence for reasonable validity in assessing fatigue in RA [2]. The MAF-GFI was selected for use in the current study. This is a multidimensional instrument specifically adapted from the items of the Piper fatigue scale for use in RA [23]. In OA, a VAS has been most widely used to measure fatigue [6, 17, 18], but the MAF-GFI has also been validated for use in OA [24].

In the present study, we aimed to identify the relative contribution of systemic inflammation on the experience of fatigue by comparing two cohorts: one with RA (inflammatory) and one OA (non-inflammatory). We also examined differences between and within these cohorts in relation to inflammation, pain, disability, joint damage and mood disturbance, in order to determine correlations between fatigue and implicated variables in both RA and OA.

Direct comparisons of fatigue in inflammatory and non-inflammatory arthritis are few in the literature. This is the first study, to our knowledge, to correlate the MAF-GFI with the disease activity score-28 joint count (DAS-28), a standard measure of disease activity in RA. It is also the first to test the correlation of fatigue with anatomical joint damage using the Sharp score.

**Methods**

A cross-sectional study was performed in a district hospital in New Zealand. A total of 206 participants were recruited from an outpatient population, 103 with RA from the rheumatology clinic and 103 with OA recruited from a primary assessment clinic, evaluating suitability for joint replacement surgery. Participants were consecutive patients meeting inclusion criteria and were enrolled over a period of 12 months.

Patients >18 years of age were invited to participate if they fulfilled either the ACR criteria for RA or had OA, as defined by pain from either or both knees and/or hips on most days of the previous 3 months, combined with radiological changes of OA. All participants were able to read and understand the questionnaires and provide informed consent. Patients were excluded from the study if they had a secondary diagnosis acknowledged as a potential cause of persistent fatigue. This included major depressive illness, chronic fatigue syndrome, fibromyalgia, uncorrected thyroid disease, Addison’s disease, pituitary disease, congestive cardiac failure, multiple sclerosis, inflammatory bowel disease, malignancy, inter-current acute infection, pregnancy or chronic infections such as HIV and viral hepatitis. Prior joint replacement surgery was not an exclusion, although in the case of subjects with OA the index joint (as identified by the patient) was required to be a native joint. There were no other exclusion criteria.

The study was approved by the Lower South Ethics Committee, Ministry of Health, New Zealand. All participants provided informed, written consent in accordance with the Declaration of Helsinki.

Disease duration was self-reported as the time since symptom onset. Current treatments, including NSAIDs, oral prednisone and DMARDs were recorded for each participant. Disease activity in RA was measured using the CRP (mg/l) and the DAS-28, composed of: a 28 tender joint count; 28 swollen joint count; CRP, and the self-reported general health on a 100 mm VAS (calculated according to the formula given at www.das-score.nl), scored 0–10, higher scores indicating worse severity. The Van der Heijde modified Sharp score was used to grade erosive damage—plain posteroanterior radiographs of the hands and feet were obtained, radiological damage was assessed by measuring erosions and joint space narrowing in 44 different joints and reported as an aggregated score ranging from 0 to 448 [25].

In OA, the WOMAC score [26] was used to measure symptom severity. Scores were subdivided into pain (WOMAC-A) (score 0–20), disability (WOMAC-C) (score 0–68) and stiffness (WOMAC-B) (score 0–8) for analysis. Standard antero-posterior radiographs of the hip and knee were taken and graded according to the Kellgren–Lawrence (KL) grading system (range 1–4) [27]. The CRP
was measured for comparison with the RA cohort. Higher scores in all these measures indicated greater disease severity.

In both cohorts, the following instruments were used. The severity of fatigue was assessed using the MAF as the total GFI. The MAF has good internal consistency in both diseases [7, 24]. The MAF-GFI scale contains 16 items measuring four dimensions of fatigue: severity, distress, degree of interference with activities of daily living and timing. The MAF-GFI scores range from 1 (no fatigue) to 50 (severe fatigue). Mean scores in healthy individuals vary over time between 15.8 and 17 [7]. Anxiety and depression were measured using the Hospital Anxiety and Depression scale (HADS), a 14-item scale with 7 items for anxiety (HADS-A) and 7 for depression (HADS-D)—scores ranged from 0 to 21 for each subscale. Higher scores indicated increasing severity and scores over 10 suggest clinically relevant mood disorders [28]. Disability was assessed using the anglicized HAQ disability index, which contains 20 questions grouped into eight categories. Each item was scored 0–3 and the sum of the scores divided by eight to give a final score of 0 (no disability) to 3 (complete disability) [29]. Sleep disturbance was measured using a 100-mm VAS with the question ‘How would you rate the average amount of sleep you have had over the last seven days?’ This VAS had no calibration marks and end descriptors ‘Full nights sleep’ and ‘No sleep at all’. A similar method has been used previously in studies in both RA and OA [6, 30]. Pain was recorded using a 100-mm VAS with the question ‘How would you rate the average amount of pain you experience from all your joints over the last seven days?’ This VAS had no calibration marks and descriptors ‘No pain’ and ‘Worst pain imaginable’. Higher VAS scores indicated greater symptom severity.

Statistical methods

Power analysis undertaken before commencement of the study indicated that to recognize a medium effect size using the MAF-GFI at 5.55 [7] while maintaining a power estimate of 0.80, a significant difference between two cohorts could be detected with a sample size of at least 50 participants in each cohort. A series of t-tests were used to compare variables between the RA and OA cohorts. Analysis of covariance (ANCOVA) was used to adjust for an interaction between HAQ score and MAF-GFI between the cohorts. Linear regression analysis was used to determine the extent to which each variable related to fatigue scores on the MAF-GFI for the two cohorts separately, while controlling for other variables including age squared to account for potential non-linear association. Statistical analysis was performed using Stata10 software (StataCorp LP: College Station, Texas, USA).

Results

The demographic characteristics of the two cohorts are reported in Table 1. The mean duration of disease in participants with RA was 14.8 years (±12.7). The majority of the participants with OA found it impossible to recall the exact onset of their arthritis and therefore this variable was omitted from all analyses. The OA cohort was older than those with RA (P < 0.0001) and had less of a female preponderance than the RA cohort, although this was non-significant [χ²(1) = 3.59, P = 0.058].

The profile of disease-modifying agents is shown in Table 1. Combinations of DMARD therapy were taken by 47.6% of patients. None of the participants were receiving biologic therapies as these were not funded in the New Zealand public health system at the time of the study. There was no association between the MAF-GFI scores and treatment with any of the drugs examined: prednisone at a dose between 5 and 10 mg daily: [mean MAF-GFI (s.d.), P-value] 25.3 (12.4), P = 0.71; MTX: 24.3 (11.8), P = 0.54; combination DMARD therapy: 24.7 (11.5), P = 0.93.

Table 2 shows a comparison of mean scores for the OA and RA cohorts. The CRP was higher in the RA group (P < 0.0001). Sleep disturbance (P < 0.0001), pain (P < 0.0001), disability (P = 0.0001) and depression (P = 0.007) were all higher in the OA cohort. Anxiety levels were similar in both the cohorts (P = 0.90).

Participants with OA rated their fatigue on the MAF-GFI as significantly greater than participants with RA (P = 0.03). This appeared to be related to a greater proportion of patients with OA experiencing moderate fatigue (45.6 %), compared with those with RA (27.2 %). These results are shown in Tables 2 and 3. However, after controlling for differences in the HAQ score, the adjusted

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA (n = 103), % or mean (s.d.)</th>
<th>OA (n = 103), % or mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58.4 (12.2)</td>
<td>66.0 (9.0)</td>
</tr>
<tr>
<td>Gender, male, %</td>
<td>29.1</td>
<td>41.7</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>14.8 (12.7)</td>
<td>–</td>
</tr>
<tr>
<td>DAS-28 (CRP)</td>
<td>3.50 (1.1)</td>
<td>–</td>
</tr>
<tr>
<td>RF (+ve), %</td>
<td>89.4</td>
<td>–</td>
</tr>
<tr>
<td>Anti-CCP (+ve), %</td>
<td>79.7</td>
<td>–</td>
</tr>
<tr>
<td>DMARD treatment*, %</td>
<td>96.1</td>
<td>0</td>
</tr>
<tr>
<td>MTX, %</td>
<td>65.0</td>
<td>0</td>
</tr>
<tr>
<td>LEF</td>
<td>14.5</td>
<td>0</td>
</tr>
<tr>
<td>Prednisone, 5–10 mg/day</td>
<td>19.4</td>
<td>0</td>
</tr>
<tr>
<td>SSZ</td>
<td>23.3</td>
<td>0</td>
</tr>
<tr>
<td>Combination two or more DMARDs</td>
<td>47.6</td>
<td>0</td>
</tr>
<tr>
<td>NSAID treatment, %</td>
<td>42.7</td>
<td>38.8</td>
</tr>
<tr>
<td>WOMAC (total)</td>
<td>–</td>
<td>53.5 (16.9)</td>
</tr>
<tr>
<td>KL score</td>
<td>–</td>
<td>3.34 (0.91)</td>
</tr>
<tr>
<td>Sharp score</td>
<td>60.9 (68.70)</td>
<td>–</td>
</tr>
<tr>
<td>Sharp score/disease duration</td>
<td>4.75 (5.12)</td>
<td>–</td>
</tr>
</tbody>
</table>

*For DMARD therapy some participants were taking combinations of agents; Anti-CCP: anti-cyclic citrullinated peptide antibody; WOMAC total score (range 0–96).
difference between OA and RA cohorts in the MAF-GFI was 1.5 U (95% CI –4.7, 8.2; \( P = 0.59 \)).

Table 4 shows the relationship between disease variables and the MAF-GFI scores separately for the RA and OA cohorts. The unstandardized regression coefficients (B-coefficients) are given and represent the independent contributions of each independent variable to the prediction of the dependent variable. Unadjusted values represent a bivariate analysis and adjusted values, those controlling for all other variables including age squared and gender. Within the RA cohort, the MAF-GFI scores were associated with both depression (\( P < 0.001 \)) and anxiety (\( P < 0.001 \)) as measured by the HADS. There was no association with any other variable although the DAS-28 approached a significant association with the MAF-GFI scores (\( P = 0.07 \)). In contrast to other studies, there was no association between the MAF-GFI and VAS pain in either group (RA: \( P = 0.43 \), OA: \( P = 0.28 \)).

Correlation coefficients demonstrated weak associations between depression in RA and two variables of particular interest: pain (\( r = 0.28 \)) and sleep disturbance (\( r = 0.11 \)).

In the OA cohort, the CRP demonstrated the strongest association with the MAF-GFI (\( P = 0.001 \)). This was a negative association, but since mean level of the CRP in this group was 4.2 mg/l and the lower limit of detection for the assay used was 4 mg/l, it is unlikely that this finding has clinical relevance. Older age showed a significant association with higher fatigue (\( P = 0.021 \)). Sleep disturbance (\( P = 0.03 \)), depression (\( P = 0.04 \)) and disability (\( P = 0.04 \)) all showed significant associations with MAF-GFI.

KL grading was not associated with fatigue but values confirmed advanced OA in this cohort with 15 subjects.

### Table 2: Comparison of variables in the OA and RA cohorts

<table>
<thead>
<tr>
<th>Variable/assessment</th>
<th>RA (n = 103) mean (s.d.)</th>
<th>OA (n = 103) mean (s.d.)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAF-GFI score</td>
<td>24.6 (11.1)</td>
<td>27.7 (10.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>VAS pain, mm</td>
<td>40.9 (26.0)</td>
<td>63.8 (22.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VAS sleep, mm</td>
<td>35.1 (28.2)</td>
<td>52.5 (25.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HAQ disability score</td>
<td>0.96 (0.65)</td>
<td>1.29 (0.56)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HADS-D</td>
<td>4.3 (3.0)</td>
<td>5.5 (3.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>HADS-A</td>
<td>5.8 (4.3)</td>
<td>5.7 (3.7)</td>
<td>0.90</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>12.1 (15.8)</td>
<td>4.2 (7.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

MAF-GFI (range 1–50); VAS pain (100 mm continuous uncalibrated line); VAS sleep disturbance (100 mm continuous uncalibrated line); HAQ (range 0–3); HADS (range 0–21 for both anxiety and depression subscales).

### Table 4: Multivariate linear regressions of the MAF-GFI scores for the RA and OA cohorts

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA Unadjusted B-coefficient</th>
<th>RA Unadjusted P-value</th>
<th>RA Adjusted B-coefficient</th>
<th>RA Adjusted P-value</th>
<th>OA Unadjusted B-coefficient</th>
<th>OA Unadjusted P-value</th>
<th>OA Adjusted B-coefficient</th>
<th>OA Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>–0.19</td>
<td>0.03</td>
<td>–0.003</td>
<td>0.930</td>
<td>–0.22</td>
<td>0.061</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>DAS-28</td>
<td>4.33</td>
<td>&lt;0.001</td>
<td>1.85</td>
<td>0.065</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>0.19</td>
<td>&lt;0.001</td>
<td>0.047</td>
<td>0.398</td>
<td>–0.34</td>
<td>0.02</td>
<td>–0.40</td>
<td>0.001</td>
</tr>
<tr>
<td>Sharp score</td>
<td>–0.02</td>
<td>0.35</td>
<td>–0.003</td>
<td>0.777</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>KL score</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.68</td>
<td>0.57</td>
<td>0.23</td>
<td>0.81</td>
</tr>
<tr>
<td>WOMAC-A</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.35</td>
<td>&lt;0.001</td>
<td>–0.001</td>
<td>0.999</td>
</tr>
<tr>
<td>WOMAC-B</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.15</td>
<td>&lt;0.001</td>
<td>–0.25</td>
<td>0.716</td>
</tr>
<tr>
<td>WOMAC-C</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.47</td>
<td>&lt;0.001</td>
<td>0.10</td>
<td>0.547</td>
</tr>
<tr>
<td>VAS sleep</td>
<td>0.12</td>
<td>0.003</td>
<td>0.05</td>
<td>0.091</td>
<td>0.17</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td>0.031</td>
</tr>
<tr>
<td>VAS pain</td>
<td>0.13</td>
<td>0.002</td>
<td>–0.029</td>
<td>0.433</td>
<td>0.16</td>
<td>0.001</td>
<td>0.02</td>
<td>0.780</td>
</tr>
<tr>
<td>HADS-D</td>
<td>2.00</td>
<td>&lt;0.001</td>
<td>1.14</td>
<td>&lt;0.001</td>
<td>1.55</td>
<td>&lt;0.001</td>
<td>0.69</td>
<td>0.044</td>
</tr>
<tr>
<td>HADS-A</td>
<td>1.48</td>
<td>&lt;0.001</td>
<td>0.80</td>
<td>&lt;0.001</td>
<td>1.46</td>
<td>&lt;0.001</td>
<td>0.47</td>
<td>0.118</td>
</tr>
<tr>
<td>HAQ</td>
<td>8.99</td>
<td>&lt;0.001</td>
<td>2.75</td>
<td>0.101</td>
<td>7.60</td>
<td>&lt;0.001</td>
<td>3.77</td>
<td>0.042</td>
</tr>
</tbody>
</table>

\( ^{a} \)Adjusted for all the other variables, plus age squared and sex; B-coefficient: unstandardized regression coefficient; MAF-GFI (range 1–50); VAS pain (100 mm continuous uncalibrated line); VAS sleep disturbance (100 mm continuous uncalibrated line); HAQ disability index (range 0–3); HADS (range 0–21 for both anxiety and depression subscales); DAS-28 (range 0–10); WOMAC-A pain (range 0–20); WOMAC-B stiffness (range 0–8); WOMAC-C disability (range 0–68); Sharp Score—Van der Heijde modified (range 0–448); KL score (range 1–4).
having scores of 1–2 (14.6%) and 88 (85.4%) having scores ≥3.

Discussion

Fatigue is a notable symptom for many patients with rheumatic disease [1]. The prevalence of fatigue is dependent upon how it is defined and measured. We used the MAF-GFI score as our principal measure; an approach supported in a review of fatigue scales used in RA [20].

In the present study, participants with both RA and OA demonstrated greater fatigue scores than a previously defined healthy control population [7]. Furthermore, fatigue scores were higher among participants with OA than those with RA, a difference explained by the greater level of functional disability noted among those with OA. In contrast, previous studies have failed to demonstrate significant differences in the severity of fatigue between a number of chronic rheumatic diseases [17, 31].

Participants with OA were recruited from a primary assessment clinic, evaluating suitability for joint replacement surgery. Since New Zealand has a low rate of joint replacement surgery in comparison to the UK and Australia [32], it might be expected that this cohort had particularly severe OA. The severity of OA in the cohort was confirmed by the demonstration of both a high mean KL radiographic grade and WOMAC score, with the latter higher than in other studies of OA [33].

In contrast, the RA cohort was typical of an outpatient cohort. Disease duration, CRP, fatigue and pain levels were similar to a cohort in the UK, although disability as measured by the HAQ score was lower [34].

Although bivariate analysis suggested an association between the MAF-GFI scores and several measured variables (Table 4), multivariate linear regression analysis, used to control for covariables, demonstrated fewer significant correlations. Remaining associations with fatigue were: HAD depression in both groups; HAD anxiety in RA and the HAQ score; CRP: VAS sleep disturbance and age in OA. Differences between the two cohorts in the relative contribution of individual variables to the experience of fatigue demonstrates the complexity of this symptom, and indicates that it is not appropriate to generalize the experience of fatigue between these two conditions.

Advancing age was associated with greater fatigue in the OA cohort, but there was no such association in the RA cohort. Similar findings in RA have been noted in previous studies [6, 15].

There was no significant association between the MAF-GFI and DAS-28 in the RA cohort. The DAS-28 score provides both absolute values for remission, and a measure of high and low disease activity [35]. The DAS-28 score has not previously been correlated with the MAF-GFI. An association between disease activity and fatigue in RA remains controversial, with some studies failing to demonstrate an association [9, 31]. In contrast, studies using biologic agents have demonstrated that significant reductions in fatigue are associated with concurrent improvements in clinical parameters [36].

No significant correlation was noted with the CRP in the RA cohort. In the OA cohort, an association between higher CRP and lower levels of fatigue is difficult to explain conceptually. However, mean levels of the CRP were low in the OA group, approaching the limits of detection by the laboratory assay and were unlikely to be of clinical relevance.

Several previous studies have used inflammatory markers (especially the ESR) to assess disease activity in RA [6, 9, 13]. However, a direct association between raised inflammatory markers and fatigue was not demonstrated in a majority of studies [6, 7]. The CRP was chosen as an inflammatory marker in the current study. There are compelling reasons to select the CRP and little value in performing both measures [37].

The severity of anatomical damage was measured by the Van der Heijde modified Sharp score in RA and the KL score in OA. No association was demonstrated between MAF-GFI and these measures in either cohort and we believe this is the first study to demonstrate this.

In contrast to previous studies [6, 9, 15, 17], fatigue was not associated with pain scores when measured either by WOMAC-C or by VAS, a finding which supports the concept that pain and fatigue are separate experiences. In clinical studies pain and fatigue should both be considered for inclusion as outcome measures [38].

Sleep disturbance, measured by VAS, correlated with fatigue in the OA cohort, but not in the RA cohort. Sleep disturbance may be a determinant of fatigue and its importance has been demonstrated previously in rheumatic disease [6]. In OA, associations between knee pain and sleep disturbance have been noted [39]. Patients with OA have also been shown to demonstrate problems with sleep onset and sleep maintenance, and early morning waking [40]. In RA, a correlation between fatigue and sleep disturbance has been demonstrated previously [41]. In the current study, a simple VAS sleep scale was employed, rather than more complex validated composite scores such as the Pittsburgh Sleep Quality Index [42] or the medical outcome sleep questionnaire [23]. However, a VAS sleep scale has been assessed as a valid instrument in RA and was more strongly associated with clinical variables in a large study [41]. Our data suggest that targeting sleep disturbance for therapeutic intervention could provide an approach to managing fatigue in patients with severe OA.

Depression had a strong relationship with fatigue in both cohorts. An association between psychological well-being and fatigue has been a consistent finding in previous studies [6, 9, 13, 15, 23]. Depression has been found to be largely independent of disease activity in RA, but correlates with self-reported pain [9, 14]. However, we found only a weak association between pain measured by the VAS scale and depression in RA in our study.

Anxiety was also associated with fatigue in the RA but not the OA cohort. Previous studies have demonstrated a strong association between depression and anxiety in RA [43, 44]. It has been suggested that fatigue may elicit anxiety regarding underlying pathology or uncompleted
tasks [44]. In comparison with other studies, our New Zealand cohort demonstrated lower scores for anxiety and depression than a randomly selected community cohort in Sweden (4.55 anxiety, depression 3.98) [45] or a population of patients with RA in the UK (7.92 anxiety, 5.64 depression) [16]. These lower scores for anxiety and depression could be related to cultural differences in attitudes to mood disturbance.

The present study does have limitations. Although adding weight to previous cross-sectional studies, the direct causal relationships of the studied variables cannot be implied from the data. For example, it is not possible to ascertain from our data whether depression influences the MAF-GFI, or whether the experience of fatigue engenders depression. A prospective longitudinal study would be of benefit in answering questions relating to causation.

The choice of an OA cohort with severe index joint disease had an influence on our results. It was initially surprising to find that participants within this cohort were more fatigued than those in the RA cohort. Repeating the study using an OA cohort recruited from the community with a more representative spread of severity would provide a point of comparison.

Assessing other variables associated with fatigue would have provided additional information of interest, in particular, measures of self-efficacy, stress, resilience and social support. Such measures have been employed in previous studies [15, 44] and may combine to provide a diverse pattern of psychosocial resilience to fatigue.

Recall bias is a concern when using questionnaires to evaluate fatigue. Patterns of fatigue vary and a J-shaped curve with levels decreasing in the morning and worsening in the evening has been reported in RA [46]. This suggests that symptom diaries, recording fatigue over the course of the day, may better reflect the experience of fatigue.

In conclusion, we have demonstrated that severe lower limb joint disease in OA is a significant cause of fatigue and its severity may exceed that seen in RA. We have demonstrated that anatomical severity evaluated using radiographic grading does not appear to influence fatigue. It follows that fatigue is independent of physical joint damage.

We have confirmed the consistent finding that depression is strongly associated with fatigue in both RA and OA. Although it has been suggested that fatigue may be a useful outcome measure in RA [2], care needs to be exercised in the interpretation of this parameter since it is subject to a variety of influences, especially depressed and anxious mood.

Based on our findings, we suggest that it is not appropriate to generalize the experience of fatigue between OA and RA, due to the disparity in the association with variables such as anxiety, sleep disturbance and disability.

Elucidating the validity of instruments for measuring fatigue in RA and the relationship with other outcome measures will help to strengthen the acceptance of fatigue as an important domain in assessment of disease impact.

Interventions targeted at helping individuals with RA or OA to cope with fatigue are likely to demonstrate wider benefits, particularly in relation to mood and sleep disturbance, and the potential for therapeutic interventions in these areas should be explored.

**Rheumatology key messages**

- Fatigue in our RA cohort is independent of other commonly measured outcomes.
- The experience of fatigue cannot be generalized between OA and RA.
- Fatigue is an important symptom in determining the impact of RA.

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