Self-reported fatigue in patients with rheumatoid arthritis who commence biologic therapy: A longitudinal study (#28575)

First submission

Editor guidance

Please submit by **18 Aug 2018** for the benefit of the authors (and your $200 publishing discount).

Structure and Criteria
Please read the 'Structure and Criteria' page for general guidance.

Custom checks
Make sure you include the custom checks shown below, in your review.

Raw data check
Review the raw data. Download from the materials page.

Image check
Check that figures and images have not been inappropriately manipulated.

Privacy reminder: If uploading an annotated PDF, remove identifiable information to remain anonymous.

Files
Download and review all files from the materials page.

5 Table file(s)
1 Raw data file(s)

Custom checks

Human participant/human tissue checks

- Have you checked the authors ethical approval statement?
- Does the study meet our article requirements?
- Has identifiable info been removed from all files?
- Were the experiments necessary and ethical?

Structure and Criteria

Structure your review

The review form is divided into 5 sections. Please consider these when composing your review:

1. **BASIC REPORTING**
2. **EXPERIMENTAL DESIGN**
3. **VALIDITY OF THE FINDINGS**
4. General comments
5. Confidential notes to the editor

You can also annotate this PDF and upload it as part of your review

When ready submit online.

Editorial Criteria

Use these criteria points to structure your review. The full detailed editorial criteria is on your guidance page.

BASIC REPORTING

- Clear, unambiguous, professional English language used throughout.
- Intro & background to show context. Literature well referenced & relevant.
- Structure conforms to PeerJ standards, discipline norm, or improved for clarity.
- Figures are relevant, high quality, well labelled & described.
- Raw data supplied (see PeerJ policy).

EXPERIMENTAL DESIGN

- Original primary research within Scope of the journal.
- Research question well defined, relevant & meaningful. It is stated how the research fills an identified knowledge gap.
- Rigorous investigation performed to a high technical & ethical standard.
- Methods described with sufficient detail & information to replicate.

VALIDITY OF THE FINDINGS

- Impact and novelty not assessed. Negative/inconclusive results accepted. *Meaningful* replication encouraged where rationale & benefit to literature is clearly stated.
- Data is robust, statistically sound, & controlled.
- Speculation is welcome, but should be identified as such.
- Conclusions are well stated, linked to original research question & limited to supporting results.

Standout reviewing tips

The best reviewers use these techniques

Tip	*Example*
Support criticisms with evidence from the text or from other sources	*Smith et al (J of Methodology, 2005, V3, pp 123) have shown that the analysis you use in Lines 241-250 is not the most appropriate for this situation. Please explain why you used this method.*
Give specific suggestions on how to improve the manuscript	*Your introduction needs more detail. I suggest that you improve the description at lines 57- 86 to provide more justification for your study (specifically, you should expand upon the knowledge gap being filled).*
Comment on language and grammar issues	*The English language should be improved to ensure that an international audience can clearly understand your text. Some examples where the language could be improved include lines 23, 77, 121, 128 – the current phrasing makes comprehension difficult.*
Organize by importance of the issues, and number your points	*1. Your most important issue* *2. The next most important item* *3. …* *4. The least important points*
Please provide constructive criticism, and avoid personal opinions	*I thank you for providing the raw data, however your supplemental files need more descriptive metadata identifiers to be useful to future readers. Although your results are compelling, the data analysis should be improved in the following ways: AA, BB, CC*
Comment on strengths (as well as weaknesses) of the manuscript	*I commend the authors for their extensive data set, compiled over many years of detailed fieldwork. In addition, the manuscript is clearly written in professional, unambiguous language. If there is a weakness, it is in the statistical analysis (as I have noted above) which should be improved upon before Acceptance.*

Self-reported fatigue in patients with rheumatoid arthritis who commence biologic therapy: A longitudinal study

Hege Selheim Rinke Corresp., [1, 2] , **Clara Beate Gram Gjesdal** [1, 3] , **Heidi Markussen** [2, 4] , **Jôrg Assmus** [5] , **Gerd Karin Natvig** [2]

[1] Department of Rheumatology, Haukeland University Hospital, Bergen, Norway
[2] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[3] Department of Clinical Science, University of Bergen, Bergen, Norway
[4] Department of Thoracic medicine, Haukeland University Hospital, Bergen, Norway
[5] Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway

Corresponding Author: Hege Selheim Rinke
Email address: hegerinke@gmail.com

Aims and objectives. To examine changes in self-reported fatigue over a twelve months period in rheumatoid arthritis patients who commence biologic treatment, and to identify possible predictors for such changes.

Background. Fatigue is a burdensome symptom for patients with rheumatoid arthritis. Despite biologics are effective in reducing disease activity, patients are still reporting fatigue.

Design. A longitudinal observational study.

Methods. A total of 48 patients were enrolled in the study. Fatigue was measured by the Fatigue Severity Scale. The independent samples T-tests were used to test gender differences and the paired samples T-tests were used to measure differences between repeated measures. Bivariate and multiple regression analyses were used to examine potential predictors for changes in fatigue, such as age, sex, Disease Activity Score 28, pain, physical and emotional well-being.

Results. Forty-seven completed the study. From baseline to 12 months follow-up fatigue decreased significantly for both women and men. Analyses of predictors were performed step-wise, and the final model included sex and physical well-being. The results from this final step showed that female sex was the only significant predictor for changes in fatigue.

Conclusion. Patients commencing biologics reported a significant reduction in fatigue. Female sex was a significant predictor of changes in fatigue.

Relevance to clinical practice. Despite improvements in pharmacological treatment, patients with rheumatoid arthritis are still reporting fatigue. This is a multifaceted health problem encompassing personal and emotional factors in addition to the clinical factors directly connected to the disease. To combat fatigue, we suggest that psychosocial forms of therapies are offered in addition to pharmacological treatment.

Title of the research paper Self-reported fatigue in patients with rheumatoid arthritis who commence biologic therapy: A longitudinal study

Authors: Hege S. Rinke 1, 2, Clara Gram Gjesdal 1, 3, Heidi Markussen 2, 4, Jürg Aßmus 5 & Gerd K. Natvig 2

1 Department of Rheumatology, Haukeland University Hospital, Bergen 2
Department of Global Public Health and Primary Care, University of Bergen, Bergen 3
Department of Clinical Science, University of Bergen, Bergen 4
Department of Thoracic Medicine, Haukeland University Hospital, Bergen 5
Centre for Clinical Research, Haukeland University Hospital, Bergen

Correspondence: Hege Selheim Rinke
hegerinke@gmail.com

Self-reported fatigue in patients with rheumatoid arthritis who commence biologic therapy: A longitudinal study

Aims and objectives. To examine changes in self-reported fatigue over a twelve months period in rheumatoid arthritis patients who commence biologic treatment, and to identify possible predictors for such changes.

Background. Fatigue is a burdensome symptom for patients with rheumatoid arthritis. Despite biologics are effective in reducing disease activity, patients are still reporting fatigue.

Design. A longitudinal observational study.

Methods. A total of 48 patients were enrolled in the study. Fatigue was measured by the Fatigue Severity Scale. The independent samples T-tests were used to test gender differences and the paired samples T-tests were used to measure differences between repeated measures. Bivariate and multiple regression analyses were used to examine potential predictors for changes in fatigue, such as age, sex, Disease Activity Score 28, pain, physical and emotional well-being.

Results. Forty-seven completed the study. From baseline to 12 months follow-up fatigue decreased significantly for both women and men. Analyses of predictors were performed step-wise, and the final model included sex and physical well-being. The results from this final step showed that female sex was the only significant predictor for changes in fatigue.

Conclusion. Patients commencing biologics reported a significant reduction in fatigue. Female sex was a significant predictor of changes in fatigue.

Relevance to clinical practice.

Despite improvements in pharmacological treatment, patients with Rheumatoid Arthritis are still reporting fatigue. This is a multifaceted health problem encompassing personal and emotional

47 factors in addition to the clinical factors directly connected to the disease. To combat fatigue, we
48 suggest that psychosocial forms of therapies are offered in addition to pharmacological
49 treatment.
50
51 Key words: rheumatoid arthritis, biologic therapy, fatigue, Fatigue Severity Scale, gender
52
53 **What does this paper contribute to the wider global clinical community?**
54 *Fatigue is one of the most burdensome symptoms from the patient perspective.
55 * The reduction in fatigue observed after twelve months was higher in women than in men
56 *Female sex was the most important predictor of changes in fatigue
57
58
59
60
61
62
63
64
65
66
67
68
69

70

71

72

73 Introduction

74 Rheumatoid arthritis (RA) is an inflammatory joint disease which may cause joint damage,
75 disability and fatigue (Scott, Wolfe, & Huizinga, 2010). RA patients experience fatigue as
76 unpredictable, overwhelming and different from normal tiredness (Feldthusen, Bjork, Forsblad-
77 d'Elia, & Mannerkorpi, 2013). A conceptual model for fatigue suggests interactions with the RA
78 disease process, personal issues, feelings, thoughts and behaviors (Hewlett, Chalder, et al.,
79 2011). Fatigue in RA is under-recognized and undertreated (Hewlett et al., 2005). Furthermore, it
80 is one of the most burdensome symptoms from the patient perspective (Kirwan et al., 2007), (van
81 Tuyl et al., 2016). Over the last decades biologic agents have caused a paradigm shift in the
82 treatment of RA, and biologics are effective in reducing disease activity, inflammation, pain and
83 joint damage in RA (Scott et al., 2010). However, patient-reported consequences of disease
84 activity may differ from the assessments made by health professionals (Studenic, Radner,
85 Smolen, & Aletaha, 2012).

86

87 Background

88 Recommendations endorsed by the European League Against Rheumatism and the American
89 College of Rheumatology encourage all clinical trials to report fatigue (Aletaha et al., 2008),
90 (Kirwan et al., 2007). Fatigue is a self-reported measure and can incorporate one single item or
91 multiple items. Furthermore, the scales can have a unidimensional or multidimensional structure.
92 The Fatigue Severity Scale (FSS) is a disease-specific questionnaire intended to assess fatigue in

multiple sclerosis and systemic lupus patients, but it is also extensively used in RA studies[1] the FSS is better at detecting changes than generic questionnaires (Hewlett, Dures, & Almeida, 2011). As fatigue in RA patients is measured by various patient-reported outcome measures (Hewlett, Dures, et al., 2011) (Pouchot et al., 2008), and as results from these measures are difficult to compare, the review below will mainly refer to research based on the FSS.

Effect of biologic therapy on fatigue

Only a few previous studies have examined the effect of biologic therapy on fatigue measured with a disease-specific scale. In a double-blinded study, patients with Primary Sjögren's syndrome received biologic therapy or placebo, and fatigue was measured using both the FSS and Visual Analogue Scale (VAS). After four weeks of treatment there was no significant reduction in fatigue in these patients (Norheim, Harboe, Goransson, & Omdal, 2012). On the other hand, another study has evaluated the effect of biologic therapy on work ability, fatigue and functional disability in RA patients after six months. In this study, fatigue was measured using the FSS and VAS, and the results demonstrated that biologics had a beneficial effect on fatigue in patients with RA (Hussain et al., 2015).

Predictors for changes in fatigue

As stated by Ahmed and colleagues, patient-reported outcomes are important as they represent information from the patient perspective that has not been interpreted by health personnel (Ahmed et al., 2012) and such measures might provide additional and different information that is relevant for both RA patients and physicians (Gossec, Dougados, & Dixon, 2015). Previous research has identified both patient-reported factors and more objective measures evaluated by health personnel as predictors for fatigue. In a review containing both cross-

116 sectional and longitudinal studies as well as several measures of fatigue, the results showed a
117 correlation between fatigue and self-reported pain, physical function and depression (Nikolaus,
118 Bode, Taal, & van de Laar, 2013). In a systematic review of cross-sectional, observational and
119 cohort studies examining psychological factors as predictors for fatigue, there was a consistent
120 correlation between self-reported mood and fatigue, and low mood was associated with increased
121 fatigue (Matcham, Ali, Hotopf, & Chalder, 2015). The most common physician-reported
122 measure of disease activity in patients with RA is the Disease Activity Scale 28 (DAS28) (van
123 Riel, 2014). To our knowledge, no previous studies including both self-reported and physician-
124 reported measures have measured fatigue using the FSS. In a previous study of both self-reported
125 and physician-reported data, results showed that disease activity, pain, sleep disturbance, and
126 mental health were related to fatigue (Thyberg, Dahlstrom, & Thyberg, 2009). A review of
127 correlations between different disease activity measures, pain and fatigue showed that pain was
128 the strongest factor associated with fatigue (Madsen, Danneskiold-Samsoe, Stockmarr, &
129 Bartels, 2016). In these studies gender has not been considered as a possible predictor for change
130 in fatigue.
131 Regarding sociodemographic data, gender differences have been observed in previous research.
132 One study found higher prevalence of RA in women than men (Barragan-Martinez et al., 2012).
133 Female patients also reported significantly higher fatigue measured by the FSS compared with
134 healthy controls (Buyuktas et al., 2015), and female participants reported more persistent fatigue
135 after four years than men did (Druce, Jones, Macfarlane, Verstappen, & Basu, 2015). In a study,
136 Thyberg et al. (2009) found that women reported more fatigue measured by VAS than men.
137 Furthermore, one study found a difference between the patient and physician assessment of

138 global disease activity, and this difference was more pronounced in women than in men
139 (Lindstrom Egholm et al., 2015).
140
141 The aims of the present study were:
142 • To examine changes in self-reported fatigue in RA-patients who commence biologic
143 treatment.
144 • To identify possible predictors (sociodemographic as well as patient-reported and health
145 personnel-reported variables) for changes in fatigue.

146 ## Methods

147 ### Design

148 This study was a longitudinal study comparing fatigue levels over 12 months. Patients were
149 assessed at baseline (T0) and after 3 (T1), 6 (T2) and 12 months (T3).
150 The study was part of an observational study to explore ultrasonographic differences in total
151 synovitis between seropositive and seronegative rheumatoid arthritis patients.
152 Inclusion criteria were as follows and the same as in the main study: 1) male or non-pregnant,
153 non-nursing female 2) age between 18 and 75 years 3) patient is classified as having RA
154 according to the 2010 American College of Rheumatology/ The European league against
155 rheumatism criteria (Aletaha et al., 2010) 4) the treating rheumatologist and the patient have
156 decided that biologic treatment is needed 5) the patient has had no prior biologic treatment 6)
157 patients is able and willing to give written informed consent and comply with the requirements
158 of the study protocol. Exclusion criteria: 1) abnormal renal function (serum creatinine > 142
159 μmol/L in female and > 168 μmol/L in male, or GFR < 40 mL/min/1.73m² 2) abnormal liver
160 function (ASAT/ALAT > 3 times normal), active or recent hepatitis, cirrhosis 3) major co-

161 morbidities like severe malignancies, severe diabetic mellitus, severe infections, uncontrollable
162 hypertension, severe cardiovascular disease (The New York Heart Association Functional Class
163 3-4) and/or severe respiratory disease 4) leukopenia and/or thrombocytopenia 5) inadequate birth
164 control, pregnancy, and/or breastfeeding 6) indications of active tuberculosis 7) psychiatric or
165 mental disorders, alcohol abuse or other abuse of substances, language barriers or other factors
166 which make adherence to the study protocol impossible.
167
168 **Data collection**
169 During the period from October 2011 to December 2014 all eligible patients were invited to
170 enter the study. A physical examination, including checking for co-morbidities and joint
171 counting, was performed by a rheumatologist. A study nurse collected clinical data, and the
172 patients completed the self-reported questionnaires. Blood tests were collected from patient
173 records. When the last enrolled patient had been followed for 12 months the study was closed.
174
175 **Treatment**
176 The patients in this study commenced their first biologic therapy (certolizumab, etanercept,
177 golimumab, infliximab or rituximab) according to standard procedures and doses.
178 38 patients were on stable doses of methotrexate 3 months before baseline and until visit T1. 6
179 patients were taking leflunomide or hydroxychloroquine, and 4 patients had no synthetic disease-
180 modifying antirheumatic drugs (DMARDs).
181 A total of 28 patients had a stable low dose of corticosteroids the last month before inclusion and
182 until visit T1. Patients were told to avoid analgesics for 24 hours prior to the visits if possible.
183

184 **Assessments**

185 Fatigue was measured using the FSS, which is a 9-item questionnaire rated on a scale from 1 to
186 7, where 1 indicates strongly disagree and 7 indicates strongly agree. The FSS contains
187 statements on the severity of fatigue, and also the effect on a person's activities and lifestyle
188 (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). The FSS is used in a number of diseases and
189 is a reliable instrument for measuring fatigue (Valko, Bassetti, Bloch, Held, & Baumann, 2008).
190 The FSS has demonstrated good psychometric properties and is one of the few measures that are
191 able to detect change over time (Whitehead, 2009).
192 Rheumatoid Arthritis Impact of Disease (RAID) was used to measure pain, physical and
193 emotional wellbeing (Gossec et al., 2009). The rating scales are from 0-10. Pain is assessed from
194 none to extreme and physical and emotional wellbeing is assessed from very good to very bad.
195 RAID has been validated (Heiberg, Austad, Kvien, & Uhlig, 2011).
196 The Disease Activity Score using 28 joint counts (DAS28) can be based on three variables:
197 Tender and swollen joint counts and ESR (Fransen, Creemers, & Van Riel, 2004). DAS28 has
198 been validated to monitor disease activity in RA (van Riel, 2014).
199

200 **Statistical analyses**

201 Descriptive statistics were used to describe sociodemographic, patient-reported and health
202 personnel-reported variables. The independent samples *t*-test was used to test for differences
203 between women and men. The paired samples *t*-test was used to test for differences between
204 measures at different points in time.
205 Linear mixed effect analyses were used to identify associations between change in fatigue level
206 and clinical variables such as DAS28, sociodemographic variables such as sex and age, and self-

reported variables such as pain and physical and emotional wellbeing. First, a 0-model containing time only was made. In step 1, to estimate the main effect and interaction effect, each predictor was put into a model containing time. The Akaikes information criterion (AIC) was used as a criterion to decide whether the model fitted the data and also to compare the models to the 0-model by measuring p-value and performing a likelihood ratio test. In step 2, significant predictors were put into a model one by one. RAID subscales were added in order of their AIC score. In step 3 only predictors contributing to the model were added.

The significance level was set to 0.05. SPSS 23 for Windows (IBM Corp., Armonk, NY) and R 3.3.0 (R Core team, 2016) with the package nlme 3.1 (Pinheiro, Bates, DebRoy, Sarkar, & R Core Team, 2016) were used for the statistical analysis.

Ethical considerations

The study was approved by the Regional Ethics committee for Medical Research (REK, 2011/490) and all the patients provided written informed consent.

Results

A total of 48 patients met the inclusion criteria, and gave consent to participate in the study. One patient was excluded after 3 months because of acute illness and need of surgery. 47 patients completed the study (Figure 1).

At baseline the patients had a median age of 55 years [range 24-73 years], and more than half of the patients (56 %) were women. The mean disease duration was 5 years (SD 7.5), [range <1- 40 years]. Sociodemographic and clinical baseline characteristics are shown in Table 1.

The mean fatigue measurements and their changes are shown in Table 2. At baseline we observed a significantly more severe fatigue for female than for male patients. The severity of fatigue decreased significantly for both women and men between baseline and visit T1 and then stabilized. This improvement was stronger for women (mean (CI) = 1.3 (0.7,1.9), $p < 0.001$) than for men, mean (CI) = 0.6 (0.8,1.2), $p = 0.026$).

As shown in Table 3 the disease activity measured by DAS28 decreased significantly between baseline and 3 months (mean (CI) = 1.4 (1.1,1.7), $p < 0.001$) and was stabile in later visits. The same development was observed for the selected RAID subscales. In the linear mixed effects model sex and RAID emotional well-being contributed significantly to the model (Step 2 in Table 4), while we did not observe any effect of DAS28 on fatigue (Step 1 in Table 4).

Analysis of predictors (Table 4) showed higher reduction in fatigue values at follow-up visit T2 (6 months) for women than men ($p = 0.019$). At follow-up visit T3 (12 months) there was a significant change in fatigue for females ($p = 0.015$). The changes in fatigue and the RAID variables pain and physical and emotional wellbeing are explained by the gender component. The change in fatigue is explained by both female sex and physical wellbeing, but in the end female sex had stronger influence than physical wellbeing and turned out to be a significant predictor for change in fatigue ($p = 0.010$).

Discussion

This study found that both female and male RA patients commencing biologic therapy reported lower levels of fatigue during treatment. Previous research has shown somewhat inconsistent results and, to our knowledge, gender differences have not been examined. In a randomized clinical trial, Norheim et al. (2012) reported no significant effect of biologics on fatigue in Sjögren

253 patients. However, a post hoc analysis showed that six out of 12 patients in the group treated
254 with biologics reported a 50% reduction in fatigue compared to one out of 13 in the placebo
255 group, and this result was significant. Another study investigated the effect of biologics on work
256 ability, functional disability and fatigue. The results from this observational study showed
257 significant improvements in fatigue after six months of biologic therapy (Hussain et al., 2015).
258 These inconsistencies may be explained by the fact that fatigue is a patient-reported symptom
259 with individual variations in severity and etiology and by different diseases studied. In some
260 patients, fatigue may persist despite biologic therapy (Emery, 2014) and the explanation for this
261 may be found in the etiology of fatigue as a symptom with multiple causes, some connected to
262 disease activity and others to personal factors (Hewlett, Chalder, et al., 2011). When RA patients
263 with fatigue were interviewed and encouraged to describe this problem in their own words, they
264 described fatigue as an experience that was always present, preventing them from finding
265 solutions to everyday problems and affecting both themselves and their social life (Bala et al.,
266 2016). A broader approach covering all aspects of this health problem is needed.
267

268 **Patient reports versus reports by health professionals** In
269 bivariate analyses disease activity and age showed insignificant associations to change in fatigue
270 at all follow-up visits. Pain showed no significant relationship with fatigue in both bivariate and
271 multivariate analyses. There was a significant association between emotional wellbeing and
272 change in fatigue at the 6-month follow-up visit in bivariate analyses and at the 12-month
273 follow-up visit in multivariate analyses. In bivariate analyses physical well-being was a
274 statistically significant predictor of change in fatigue, but in multivariate analyses only the 3-
275 month follow-up visit showed a significant change in fatigue. Female sex was a significant

predictor in both bivariate and multivariate analyses. As far as we know, in previous research sex has rarely been a variable in analyses of predictors of change in fatigue and the results of this study may be difficult to compare to other studies. Still, the results of the patient and health personnel-reported outcomes in this study might be comparable. In a systematic review, Madsen et al. (2016) found that disease activity was positively related to fatigue when pain was not considered, and that pain was the dominating factor related to fatigue. However, in these studies disease activity was measured using different components of DAS28, and the various components of DAS28 have different weightings, with some of them being more related to inflammation than others. It might therefore be difficult to compare the results of these studies (Madsen et al., 2016).

A gender perspective on fatigue in rheumatoid arthritis

In this study women reported statistically significantly higher fatigue at baseline than men. During the study mean fatigue score was higher in women at all follow-up visits. Previous work has shown that women report higher values of fatigue than men (Rat et al., 2012), (Thyberg et al., 2009), and several factors such as genetic and hormonal factors and other exposures that may be experienced differently by women and men have been suggested as explanations for the difference between men and women in terms of RA disease impact (van Vollenhoven, 2009). Pain and related measurements are often discussed as being non-sex-neutral. In a review, somatic symptom reporting in women and men has been examined. Results showed that women reported more numerous, more intense and more frequent bodily symptoms than men (Barsky, Peekna, & Borus, 2001). Moreover, women and men may react differently to treatment. In a register-based observational study of predictors of response to biologic therapy, there was a lower remission rate among female RA patients (Hyrich, Watson, Silman, & Symmons, 2006). Furthermore, in a

299 study of fibromyalgia patients undergoing cognitive-behavioral therapy, results showed
300 differences in the responses to treatment between women and men in pain and sleep related
301 variables (Lami et al., 2016). Multivariate analyses showed that change in fatigue is
302 explained by both female sex and physical wellbeing. Still, in the final model only female sex
303 turned out to be a significant predictor for change in fatigue.
304
305 **Limitations**
306 This study is a cohort study, without a control group. Therefore, it is difficult to determine
307 whether biologic therapy affects fatigue or not. On the other hand, the patients in the study had
308 tried standard treatment with synthetic DMARDs before commencing biologics. The patients'
309 level of fatigue was followed up for twelve months, and data collection was performed four
310 times, and this may provide valuable insight into how fatigue occurs. Furthermore, the number of
311 participants is small and they are all recruited from the same Rheumatology department.
312 However, the participants were recruited consecutively and were all in need of their first biologic
313 treatment, and had no major co-morbidities. The patients in the study live along the west coast of
314 Norway, but we assume the selection is not very different from the majority of RA patients
315 living in other parts of the country as the Norwegian population is rather homogeneous.
316

317 ## Conclusion

318 Female RA patients commencing biologics report reductions in fatigue after 3 and 6 months.
319 After 12 months there is a slight increase in the fatigue level. Male RA patients report reductions
320 in fatigue after 3 and 12 months. When comparing sociodemographic, patient-reported and
321 health personnel-reported variables, female sex was a significant predictor of changes in fatigue.

This result is important and may indicate gender differences in the impact of RA. Further research is needed in order to understand the complexity of fatigue and to evaluate non-pharmacological treatment.

Relevance to clinical practice

Fatigue is a burdensome symptom in RA patients, and despite improvements in the pharmacological treatment of RA, patients are still reporting fatigue (van Hoogmoed et al., 2013), (Druce, Jones, Macfarlane, & Basu, 2015), (Madsen et al., 2016). Therefore, additional therapies are needed to combat fatigue. These therapies should take into account that fatigue is a multifaceted health problem encompassing personal and emotional factors in addition to the clinical factors directly connected to the disease.

In a review of non-pharmacological interventions for fatigue, psychosocial interventions and physical activity provided benefits in relation to fatigue in adults with RA (Cramp et al., 2013). Furthermore, a nurse-led patient education program found positive effect on global wellbeing in patients with chronic inflammatory polyarthritis after 12 months (Gronning, Rannestad, Skomsvoll, Rygg, & Steinsbekk, 2014).

References

Ahmed, S., Berzon, R. A., Revicki, D. A., Lenderking, W. R., Moinpour, C. M., Basch, E., . . . Wu, A. W. (2012). The use of patient-reported outcomes (PRO) within comparative effectiveness research: implications for clinical practice and health care policy. *Med Care, 50*(12), 1060-1070. doi: 10.1097/MLR.0b013e318268aaff

Aletaha, D., Landewe, R., Karonitsch, T., Bathon, J., Boers, M., Bombardier, C., . . . Felson, D. (2008). Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Arthritis Rheum, 59*(10), 1371-1377. doi: 10.1002/art.24123

Aletaha, D., Neogi, T., Silman, A. J., Funovits, J., Felson, D. T., Bingham, C. O., 3rd, . . . Hawker, G. (2010). 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum, 62*(9), 2569-2581. doi: 10.1002/art.27584

Bala, S. V., Samuelson, K., Hagell, P., Fridlund, B., Forslind, K., Svensson, B., & Thome, B. (2016). Living with persistent rheumatoid arthritis: a BARFOT study. *J Clin Nurs*. doi: 10.1111/jocn.13691

Barragan-Martinez, C., Amaya-Amaya, J., Pineda-Tamayo, R., Mantilla, R. D., Castellanos-de la Hoz, J., Bernal-Macias, S., . . . Anaya, J. M. (2012). Gender differences in Latin-American patients with rheumatoid arthritis. *Gend Med, 9*(6), 490-510.e495. doi: 10.1016/j.genm.2012.10.005

Barsky, A. J., Peekna, H. M., & Borus, J. F. (2001). Somatic Symptom Reporting in Women and Men. *J Gen Intern Med, 16*(4), 266-275. doi: 10.1046/j.1525-1497.2001.00229.x

Buyuktas, D., Hatemi, G., Yuksel-Findikoglu, S., Ugurlu, S., Yazici, H., & Yurdakul, S. (2015). Fatigue is correlated with disease activity but not with the type of organ involvement in Behcet's syndrome: a comparative clinical survey. *Clin Exp Rheumatol, 33*(6 Suppl 94), S107-112.

Cramp, F., Hewlett, S., Almeida, C., Kirwan, J. R., Choy, E. H., Chalder, T., . . . Christensen, R. (2013). Non-pharmacological interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev*(8), Cd008322. doi: 10.1002/14651858.CD008322.pub2

Druce, K. L., Jones, G. T., Macfarlane, G. J., & Basu, N. (2015). Patients receiving anti-TNF therapies experience clinically important improvements in RA-related fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Rheumatology (Oxford), 54*(6), 964-971. doi: 10.1093/rheumatology/keu390

Druce, K. L., Jones, G. T., Macfarlane, G. J., Verstappen, S. M., & Basu, N. (2015). The Longitudinal Course of Fatigue in Rheumatoid Arthritis: Results from the Norfolk Arthritis Register. *J Rheumatol, 42*(11), 2059-2065. doi: 10.3899/jrheum.141498

Emery, P. (2014). Why is there persistent disease despite biologic therapy? Importance of early intervention. *Arthritis Res Ther, 16*(3), 115. doi: 10.1186/ar4594

Feldthusen, C., Bjork, M., Forsblad-d'Elia, H., & Mannerkorpi, K. (2013). Perception, consequences, communication, and strategies for handling fatigue in persons with rheumatoid arthritis of working age--a focus group study. *Clin Rheumatol, 32*(5), 557-566. doi: 10.1007/s10067-012-2133-y

Fransen, J., Creemers, M. C., & Van Riel, P. L. (2004). Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. *Rheumatology (Oxford), 43*(10), 1252-1255. doi: 10.1093/rheumatology/keh297

Gossec, L., Dougados, M., & Dixon, W. (2015). Patient-reported outcomes as end points in clinical trials in rheumatoid arthritis. *RMD Open, 1*(1), e000019. doi: 10.1136/rmdopen-2014-000019

Gossec, L., Dougados, M., Rincheval, N., Balanescu, A., Boumpas, D. T., Canadelo, S., . . . Kvien, T. K. (2009). Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. *Ann Rheum Dis, 68*(11), 1680-1685. doi: 10.1136/ard.2008.100271

Gronning, K., Rannestad, T., Skomsvoll, J. F., Rygg, L. O., & Steinsbekk, A. (2014). Long-term effects of a nurse-led group and individual patient education programme for patients with

chronic inflammatory polyarthritis - a randomised controlled trial. *J Clin Nurs, 23*(7-8), 1005-1017. doi: 10.1111/jocn.12353

Heiberg, T., Austad, C., Kvien, T. K., & Uhlig, T. (2011). Performance of the Rheumatoid Arthritis Impact of Disease (RAID) score in relation to other patient-reported outcomes in a register of patients with rheumatoid arthritis. *Ann Rheum Dis, 70*(6), 1080-1082. doi: 10.1136/ard.2010.143032

Hewlett, S., Chalder, T., Choy, E., Cramp, F., Davis, B., Dures, E., . . . Kirwan, J. (2011). Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology (Oxford), 50*(6), 1004-1006. doi: 10.1093/rheumatology/keq282

Hewlett, S., Cockshott, Z., Byron, M., Kitchen, K., Tipler, S., Pope, D., & Hehir, M. (2005). Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. *Arthritis Rheum, 53*(5), 697-702. doi: 10.1002/art.21450

Hewlett, S., Dures, E., & Almeida, C. (2011). Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). *Arthritis Care Res (Hoboken), 63 Suppl 11*, S263-286. doi: 10.1002/acr.20579

Hussain, W., Janoudi, N., Noorwali, A., Omran, N., Baamer, M., Assiry el, H., . . . Almoallim, H. (2015). Effect of Adalimumab on Work Ability Assessed in Rheumatoid Arthritis Disease Patients in Saudi Arabia (AWARDS). *Open Rheumatol J, 9*, 46-50. doi: 10.2174/1874312901409010046

Hyrich, K. L., Watson, K. D., Silman, A. J., & Symmons, D. P. (2006). Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford), 45*(12), 1558-1565. doi: 10.1093/rheumatology/kel149

Kirwan, J. R., Minnock, P., Adebajo, A., Bresnihan, B., Choy, E., de Wit, M., . . . Hewlett, S. (2007). Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol, 34*(5), 1174-1177.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol, 46*(10), 1121-1123.

Lami, M. J., Martinez, M. P., Sanchez, A. I., Miro, E., Diener, F. N., Prados, G., & Guzman, M. A. (2016). Gender Differences in Patients with Fibromyalgia Undergoing Cognitive-Behavioral Therapy for Insomnia: Preliminary Data. *Pain Pract, 16*(2), E23-34. doi: 10.1111/papr.12411

Lindstrom Egholm, C., Krogh, N. S., Pincus, T., Dreyer, L., Ellingsen, T., Glintborg, B., . . . Hetland, M. L. (2015). Discordance of Global Assessments by Patient and Physician Is Higher in Female than in Male Patients Regardless of the Physician's Sex: Data on Patients with Rheumatoid Arthritis, Axial Spondyloarthritis, and Psoriatic Arthritis from the DANBIO Registry. *J Rheumatol, 42*(10), 1781-1785. doi: 10.3899/jrheum.150007

Madsen, S. G., Danneskiold-Samsoe, B., Stockmarr, A., & Bartels, E. M. (2016). Correlations between fatigue and disease duration, disease activity, and pain in patients with rheumatoid arthritis: a systematic review. *Scand J Rheumatol, 45*(4), 255-261. doi: 10.3109/03009742.2015.1095943

Matcham, F., Ali, S., Hotopf, M., & Chalder, T. (2015). Psychological correlates of fatigue in rheumatoid arthritis: a systematic review. *Clin Psychol Rev, 39*, 16-29. doi: 10.1016/j.cpr.2015.03.004

Nikolaus, S., Bode, C., Taal, E., & van de Laar, M. A. (2013). Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. *Arthritis Care Res (Hoboken), 65*(7), 1128-1146. doi: 10.1002/acr.21949

Norheim, K. B., Harboe, E., Goransson, L. G., & Omdal, R. (2012). Interleukin-1 inhibition and fatigue in primary Sjogren's syndrome--a double blind, randomised clinical trial. *PLoS One, 7*(1), e30123. doi: 10.1371/journal.pone.0030123

Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., & R Core Team. (2016). Linear and Nonlinear Mixed Effects Models (Version 3.1-127). Retrieved from http://CRAN.R-project.org/package=nlme>

Pouchot, J., Kherani, R. B., Brant, R., Lacaille, D., Lehman, A. J., Ensworth, S., . . . Liang, M. H. (2008). Determination of the minimal clinically important difference for seven fatigue measures in rheumatoid arthritis. *J Clin Epidemiol, 61*(7), 705-713. doi: 10.1016/j.jclinepi.2007.08.016

R Core team. (2016). R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from https://www.R-_project.org/

Rat, A. C., Pouchot, J., Fautrel, B., Boumier, P., Goupille, P., & Guillemin, F. (2012). Factors associated with fatigue in early arthritis: results from a multicenter national French cohort study. *Arthritis Care Res (Hoboken), 64*(7), 1061-1069. doi: 10.1002/acr.21647

Scott, D. L., Wolfe, F., & Huizinga, T. W. (2010). Rheumatoid arthritis. *Lancet, 376*(9746), 1094-1108. doi: 10.1016/s0140-6736(10)60826-4

Studenic, P., Radner, H., Smolen, J. S., & Aletaha, D. (2012). Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum, 64*(9), 2814-2823. doi: 10.1002/art.34543

Thyberg, I., Dahlstrom, O., & Thyberg, M. (2009). Factors related to fatigue in women and men with early rheumatoid arthritis: the Swedish TIRA study. *J Rehabil Med, 41*(11), 904-912. doi: 10.2340/16501977-0444

Valko, P. O., Bassetti, C. L., Bloch, K. E., Held, U., & Baumann, C. R. (2008). Validation of the fatigue severity scale in a Swiss cohort. *Sleep, 31*(11), 1601-1607.

van Hoogmoed, D., Fransen, J., Repping-Wuts, H., Spee, L., Bleijenberg, G., & van Riel, P. L. (2013). The effect of anti-TNF-alpha vs. DMARDs on fatigue in rheumatoid arthritis patients. *Scand J Rheumatol, 42*(1), 15-19. doi: 10.3109/03009742.2012.709878

van Riel, P. L. (2014). The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28). *Clin Exp Rheumatol, 32*(5 Suppl 85), S-65-74.

van Tuyl, L. H., Sadlonova, M., Hewlett, S., Davis, B., Flurey, C., Goel, N., . . . Boers, M. (2016). The patient perspective on absence of disease activity in rheumatoid arthritis: a survey to identify key domains of patient-perceived remission. *Ann Rheum Dis*. doi: 10.1136/annrheumdis-2016-209835

van Vollenhoven, R. F. (2009). Sex differences in rheumatoid arthritis: more than meets the eye. *BMC Med, 7*, 12. doi: 10.1186/1741-7015-7-12

Whitehead, L. (2009). The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. *J Pain Symptom Manage, 37*(1), 107-128. doi: 10.1016/j.jpainsymman.2007.08.019

Table 1(on next page)

Study population

Flow chart: Study population

Figure 1
Flow chart: Study population

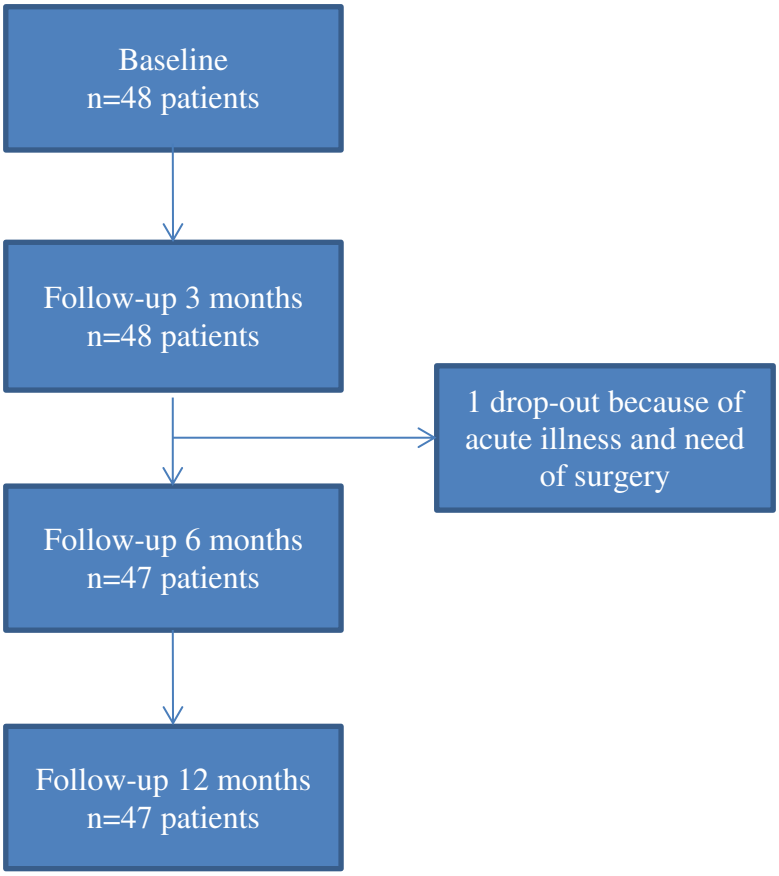

Table 2(on next page)

Sociodemographic and clinical characteristics

Sociodemographic characteristics such as age, sex, civil status, children living at home, occupational activity.

Clinical characteristics such as disease duration, rheumatoid factor, anti-cyclic citrullinated peptide, erythrocyte sedimentation rate, C-reactive protein, Disease Activity Score of 28 joints, Fatigue Severity Scale, Rheumatoid Arthritis Impact of Disease.

Table 1 Sociodemographic and clinical characteristics

Sociodemographic characteristics	*n*=48
Age, years, median (range)	55.0 [24-73]
Sex, female, n (%)	27 (56%)
Married/living with partner, n (%)	34 (71%)
Children living at home, n (%)	22 (46%)
Working or studying (full-time or part-time), n (%)	24 (50%)
Working or studying patients on sick leave, n (%)	10 (21%)
Disability benefits (full-time or part-time), n (%)	10 (21%)
Retired, n (%)	4 (8%)
Clinical characteristics	
Disease duration, years, mean (SD)	5.0 (7.5)
RF, n (%)	33 (69%)
Anti-CCP, n (%)	38 (79%)
ESR (mm/h), median (range)	22.5 [0-75]
CRP (mg/L), median (range)	9.0 [0-58]
Prednisolon dosage, mean (SD)[a]	6.0 (3.2)
Methotrexate dosage, mean (SD)[b]	20.0 (4.8)
FSS, (1-7), mean (SD)[c]	4.4 (1.5)
DAS28, mean (SD)	4.5 (1.2)
RAID - pain, mean (SD)[d]	5.5 (2.1)
RAID - emotional well-being, mean (SD)[e]	3.9 (2.1)
RAID - physical well-being, mean (SD)[d]	4.9 (1.9)

RF, rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; FSS, Fatigue Severity Scale; RAID, Rheumatoid Arthritis Impact of Disease

[a]n=28, [b]n=38, [c]n=47, [d]n=45, [e]n=44

Table 3(on next page)

Changes in fatigue, and gender differences

Changes in fatigue, and gender differences

Table 2 Mean, 95% confidence intervals and p-values of changes in fatigue during the study, and test of differences between women and men

		Women				Men				FSS difference
		FSS		FSS change from T0		FSS		FSS change from T0		Men/women
Time point	Missing	n	Mean (95% CI)	Mean (95% CI)	p	n	Mean (95% CI)	Mean (95% CI)	p	p
Baseline (T0)	1	26	5.0 (4.5,5.5)	-	-	21	3.6 (2.9,4.3)	-	-	0.001*
3 months (T1)	0	27	3.7 (3.1,4.4)	1.3 (0.7,1.9)	<0.001†	21	3.0 (2.3,3.6)	0.6 (0.8,1.2)	0,026†	0.113*
6 months (T2)	0	27	3.4 (2.7,4.1)	1.6 (0.9,2.3)	<0.001†	20	3.0 (2.3,3.7)	0.6 (-0.3,1.5)	0,155†	0.368*
12 months (T3)	2	25	3.7 (2.9,4.4)	1.4 (0.7,2.0)	<0.001†	20	2.7 (1.9,3.5)	0.9 (0.1,1.6)	0,024†	0.078*

FSS, Fatigue severity scale, scale 0-7: lower scores represent less fatigue
Confidence interval, CI
† paired *t*-test
**t*-test

Table 4(on next page)

Disease activity, pain, physical and emotional well-being during the one-year observation study of fatigue, including both women and men

Disease activity, pain, physical and emotional well-being during the one-year observation study of fatigue, including both women and men

Table 3 Mean changes, 95% confidence intervals and *p*-values during the one-year observation study of fatigue, including both women and men

Measure	*T*1: change from *T*0		*T*2: change from *T*0		*T*3: change from *T*0	
	Mean (95% CI)	*p*	Mean (95% CI)	*p*	Mean (95 CI)	*p*
DAS28	1.4 (1.1,1.7)	< 0.001†	1.4 (1.1,1.8)	< 0.001†	1.6 (1.3,1.9)	< 0.001†
RAID pain[1]	2.4 (1.6,3.3)	< 0.001†	2.2 (2.8,0.4)	< 0.001†	3.2 (2.3,4.0)	< 0.001†
RAID physical well-being[2]	1.8 (1.1,2.5)	< 0.001†	2.0 (1.2,2.7)	< 0.001†	2.3 (1.5,3.1)	< 0.001†
RAID emotional well-being[2]	1.4 (0.7,2.1)	< 0.001†	1.7 (1.0,2.4)	< 0.001†	1.3 (0.3,2.2)	0.012†

*T*0: before the intervention; *T*1: after three months; *T*2: after six months; *T*3: after twelve months
[1]Scale 0-10: lower scores represent less pain
[2]Scale 0-10: lower scores represent more well-being
DAS28, Disease activity score 28
RAID, Rheumatoid Arthritis Impact of Disease
Confidence interval, CI
† paired *t*-test

Table 5(on next page)

Predictors of fatigue: Mean changes, 95% confidence intervals and *p* -values, including both women and men

Predictors of fatigue. Model 1 with one predictor (main effect and interaction). Model 2 including sex, RAID physical well-being, RAID emotional well-being and RAID pain. Model 3 including sex and RAID physical well-being. Mean changes, 95% confidence intervals and *p* -values, including both women and men

Table 4 Predictors of fatigue: Mean changes, 95% confidence intervals and *p*-values, including both women and men

		Step 1[1]		Step 2[2]		Final model[3]	
Predictor	**Effect type**	**B (95%CI)**	**p-value**	**B (95%CI)**	**p-value**	**B (95%CI)**	**p-value**
DAS28	Main effect	0.06 (-0.26, 0.38)	,706	-	-	-	-
	Effect change: BL -> 3 months	0.34 (-0.09, 0.76)	,126	-	-	-	-
	Effect change: BL -> 6 months	0.13 (-0.32, 0.59)	,569	-	-	-	-
	Effect change: BL -> 12 months	-0.02 (-0.46, 0.43)	,937	-	-	-	-
Age	Main effect	-0.04 (-0.08, 0)	,081	-	-	-	-
	Effect change: BL -> 3 months	0 (-0.04, 0.04)	,856	-	-	-	-
	Effect change: BL -> 6 months	0.03 (-0.02, 0.07)	,234	-	-	-	-
	Effect change: BL -> 12 months	0.02 (-0.03, 0.06)	,450	-	-	-	-
Sex	**Main effect**	**1.49 (0.54, 2.43)**	**,003**	**1.27 (0.34, 2.2)**	**,013**	**1.29 (0.36, 2.23)**	**,010**
	Effect change: BL -> 3 months	-0.56 (-1.45, 0.34)	,235	0.09 (-0.17, 0.34)	,524	0.12 (-0.08, 0.32)	,255
	Effect change: BL -> 6 months	-1.13 (-2.05, -0.21)	,019	0.03 (-0.16, 0.22)	,802	-0.57 (-1.46, 0.32)	,220
	Effect change: BL -> 12 months	**-0.58 (-1.52, 0.36)**	**,236**	**0.04 (-0.16, 0.25)**	**,687**	**-1.19 (-2.11, -0.27)**	**,015**
RAID	Main effect	0.2 (0.01, 0.39)	,047	-0.69 (-1.56, 0.18)	,144	-0.38 (-1.31, 0.55)	,440
physical	Effect change: BL -> 3 months	0.13 (-0.13, 0.38)	,336	-1.15 (-2.03, -0.28)	,016	0.19 (-0.06, 0.45)	,155
well-being	Effect change: BL -> 6 months	0.04 (-0.21, 0.28)	,773	-0.38 (-1.27, 0.5)	,423	0.14 (-0.11, 0.4)	,284
	Effect change: BL -> 12 months	-0.06 (-0.32, 0.2)	,649	0.15 (-0.19, 0.49)	,418	0.02 (-0.25, 0.28)	,912
RAID	Main effect	0.14 (-0.03, 0.31)	,113	-0.15 (-0.54, 0.23)	,464	-	-
emotional	Effect change: BL -> 3 months	0.16 (-0.08, 0.39)	,199	-0.12 (-0.52, 0.27)	,561	-	-
well-being	Effect change: BL -> 6 months	0.31 (0.07, 0.56)	,016	0.09 (-0.21, 0.39)	,591	-	-
	Effect change: BL -> 12 months	0.02 (-0.2, 0.23)	,882	0.39 (0.09, 0.68)	,015	-	-
RAID	Main effect	0.1 (-0.08, 0.29)	,283	0.04 (-0.26, 0.35)	,782	-	-
pain	Effect change: BL -> 3 months	0.08 (-0.17, 0.32)	,540	0.01 (-0.25, 0.28)	,919	-	-
	Effect change: BL -> 6 months	0.14 (-0.1, 0.38)	,257	0.11 (-0.23, 0.45)	,541	-	-
	Effect change: BL -> 12 months	0.08 (-0.19, 0.35)	,552	0.14 (-0.18, 0.46)	,422	-	-

[1]Model with one predictor (main effect and interaction).[2]Model including sex, RAID physical well-being, RAID emotional well-being, RAID pain.[3]Model including sex, RAID physical well-being

BL, baseline; CI, confidence interval; DAS28, Disease Activity Score of 28 joints; RAID, Rheumatoid Arthritis Impact of Disease