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ORIGINAL REPORT

FACTORS RELATED TO FATIGUE IN WOMEN AND MEN WITH EARLY RHEUMATOID ARTHRITIS: THE SWEDISH TIRA STUDY

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Objective: **To study whether there are differences between women and men with regard to the reported level of fatigue, to explore the strength of the relations between fatigue and disease activity, pain, sleep disturbance, mental health, and activity limitation in early rheumatoid arthritis, and to explore the consistency of such findings.**

Design: **Analyses and comparisons of cross-sectional data.**

Subjects: **Two hundred and seventy-six patients, 191 women and 85 men, with early rheumatoid arthritis were included.**

Methods: **Patients were examined with respect to 28-joint count disease activity score, and disability variables reflecting pain, sleep disturbance, fatigue, mental health, and activity limitation, at follow-ups at 1, 2 and 3 years after diagnosis.**

Results: **Women reported somewhat more fatigue than men. Fatigue was closely and rather consistently related to disease activity, pain and activity limitation, and also to mental health and sleep disturbance.**

Conclusion: **Although this study does not permit conclusions to be drawn about causal directions, statistical relationships may be related to clinical conceptions about causation: when disease activity can be significantly reduced by pharmacological treatment this may have a positive effect on fatigue. Specific treatment with respect to the mentioned disability aspects that are related to fatigue is also a clinically reasonable strategy.**

Key words: early rheumatoid arthritis, fatigue, sleep disturbance, sex, regression analysis.

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INTRODUCTION

Rheumatoid arthritis (RA) has a prevalence of approximately 0.5–0.7% in the adult Swedish population and a yearly incidence of 25/100,000 (1, 2). RA often leads to disability, even early in the course of the disease, and women report more activity limitation than men (3, 4). Regarding different aspects of the disease process and the corresponding disability, a growing number of variables are taken into consideration and communicated between physicians, nurses and rehabilitation professionals encountered in dealing with these problems (5, 6). The increased storing of data on diverse aspects of disease, health, functioning and disability has a number of implications for clinical reasoning. It is important to study how professionals use and interpret the information held in such extensive medical records, for their reasoning and decisions about interventions (7). To support such clinical interpretations of data, conceptual as well as empirical analyses are necessary in order to clarify how relevant variables are related to each other (5). If such questions can be clarified, it may be possible to develop clinically useful systems for decision support (8).

Among the variables that are relevant in RA, fatigue is now considered as a common and disabling problem (9–12). Because there are no suitable direct interventions on fatigue, it is valuable to know how fatigue is related to other aspects of disease and disability. Although fatigue has been related to disease activity, pain, sleep disturbance, mental health, and activity limitation, little is known about the relative strengths and the temporal consistency of these relations during the course of RA. According to a present understanding, RA is an inflammatory process causing pain, fatigue, activity limitation, and secondary psychological distress. It is reasonable to assume that the disease process *per se*, as well as its consequences in terms of pain, activity limitation and mental health problems, are contributing causes of fatigue (13–16). The inflammatory process, as reflected by cytokines, may be one cause of sleep disturbance and fatigue (17). In addition, pain is a predictor of sleep problems and, together with psychological reactions, these factors are probably parts of the causal mechanisms of fatigue (18, 19). When the social dimension and the conceptual complexity of activity and participation are taken into consideration (5, 20), the causal mechanisms of activity limitation are difficult to capture. Activity limitation has been found to predict depression (3), and it is reasonable to assume that reduced physical capacity in combination with environmental barriers will make the performance of different activities fatiguing, and fatigue may, in its turn, lead to limited performance of activities and participation restrictions, such as work disability (9).

In persons with RA and an average age of 67 years, Belza et al. (14) found that women reported more fatigue than men,

and discussed that they typically do more household work as a possible explanation. In somewhat younger groups, Pollard et al. (19) found no relation between sex and fatigue, in contrast to Huyser et al. (21) who found that females reported more fatigue, and Wolfe (15) who found slightly more fatigue in women compared with men. Although general gender-related differences in the reporting of symptoms have been found (22), and men may tend to underestimate their activity limitations (23), we have found that the more severe activity limitations reported by women with RA are partly related to differences in grip force (4). However, it is still not clear if women report different levels of fatigue compared with men.

Pollard et al. (19) concluded that pain, activity limitation, and mental health are closely related to fatigue, but that the association between fatigue and disease activity is secondary. Similarly to Pollard et al. (19), in patients with a long duration of RA, but with a disproportionately male sample, Huyser et al. (21) could not find any strong relation between disease activity and fatigue, but suggested that such a counterintuitive result may be a statistical artefact due to inter-correlation among predictors. Thus, it remains to be clarified how disease activity and the discussed disability aspects are related to the level of fatigue.

The analysis of the relationship between different aspects of disease and disability in RA is often performed in terms of co-variation in cross-sectional data because various clinical interventions related to the specific needs of the individual patients make the study of causal mechanisms complicated (24). Although complicated, questions about the relationship between fatigue and other aspects of disease and disability have to be dealt with in clinical practice, for example in decisions about different alternatives within an extensive repertoire of possible multi-professional interventions, and in medico-legal statements with respect to, for example, the role of the disease as a cause of work disability (25). To support clinical reasoning, a possible initial step is to explore the statistical relations between relevant variables in well-defined cross-sectional data, and an objective of this study was to explore factors assumed to explain fatigue in women and men. Many studies in RA have been conducted in patients with a long duration of the disease, but our research programme is focused on patients with early RA (4). One important reason for a focus on early RA is that the treatment strategy has recently been changed to early interventions. Another reason is that many patients suffer from socially important participation restrictions, such as work disability, even early in the disease process (26).

The primary aims of this study were to analyse whether there are differences between women and men with regard to the reported level of fatigue and the related variables reflecting disease activity and disability, and to explore the strength of the relations between fatigue and disease activity, pain, sleep disturbance, mental health, and activity limitation, in cross-sectional data in early RA. A secondary aim was to explore the consistency of findings in cross-sectional data, by using different sets of follow-up data from the first years after diagnosis.

METHODS

The Swedish TIRA project

The present study is associated with the ongoing multi-centre early arthritis project with the Swedish acronym TIRA (27). The purpose of the TIRA project was to establish routines for early diagnosis and multi-professional interventions, and to collect research data in order to improve the knowledge basis of clinical decisions. Over a period of 27 months, 1996–98, a total of 320 patients with recent-onset (≤ 1 year) RA were included in the TIRA-1 cohort. The patients fulfilled ≥ 4/7 RA classification criteria (28) *or* at least: morning stiffness ≥ 60 min, symmetrical arthritis, and arthritis of small joints. The patients were assessed regarding genetics, disease activity, disability and health economics at inclusion and at 3, 6, 12 months after inclusion and thereafter yearly to the 8 years follow-up. At all visits the patients met a physician, an occupational therapist and a physiotherapist, respectively. Data used in this study was a part of data collected at the regular TIRA follow-ups at 12 months (M12), 24 months (M24), and 36 months after inclusion (M36).

Study group

The 276 patients, 191 women with a mean age at inclusion of 54 years (standard deviation (SD) 15), and 85 men with a mean age of 58 years (SD 14), remaining in the TIRA-1 cohort at M36 were included in the present study. The women were significantly younger than the men ($p < 0.05$, 95% confidence intervals (CI): 51–56 years vs 55–61 years at inclusion). The mean age of the 44 patients (24 women and 20 men) who dropped out between inclusion and M36 was significantly higher ($p < 0.001$) than the study group, i.e. 64 compared with 55 years, but there were no differences between these 2 groups with respect to the disease activity or the disability variables described below.

Disease activity and disability

Disease activity was assessed according to the 28-joint count Disease Activity Score (DAS-28) (29). Pain was reported on a 100-mm visual analogue scale (VAS), where 0 represents no pain and 100 mm represents worst possible pain (30). Sleep disturbance and fatigue were reported on VAS, where 0 represented no and 100 mm worst possible sleep disturbance and fatigue, respectively. The VAS assessments of pain, sleep disturbance and fatigue referred to "these last seven days". Fatigue was reported at M12, M24 and M36 only, while the other variables were recorded at all follow-ups. Mental health was reported according to the Mental Health part of the standard Swedish version of Short Form 36 (SF-36), scored 0–100, where 100 represents best possible mental health (31). Activity limitation was reported according to the Swedish version of the Health Assessment Questionnaire (HAQ), with a score between 0 corresponding to "no difficulty" and 3 corresponding to "unable to do" (32).

Interventions

The patients were offered interventions, such as pharmacological treatment, physiotherapy, occupational therapy and social counselling, at an individual schedule depending on repeated clinical assessments during the study period. Thus, the individual schedule included additional clinical follow-ups when necessary. In addition to individualized interventions, a patient education programme was offered to all patients during the period between M12 and M24, although the content of this programme varied somewhat between the participating units. Ongoing medication was registered at all visits. There were no differences between women and men regarding the proportion of patients taking non-steroid anti-inflammatory drugs (NSAIDs) or disease-modifying anti-inflammatory drugs (DMARDs) at M12, M24, and M36, respectively.

Statistics

Means and SD were calculated and 95% CI were used. The independent samples *t*-test was used to test differences between women and men, and the paired samples *t*-test was used to test differences be-

Table I. *Descriptives, mean values, 95% confidence intervals (95% CI), of disease activity and disability at 12 months (M12), 24 months (M24), and 36 months (M36) after inclusion, and test of differences between women and men*

	Women			Men			Test		
Disease activity and disability	Mean	95% CI	*n*	Mean	95% CI	*n*	*t*	*df*	*p*
M12									
Disease Activity (DAS-28 score)	3.86	3.64–4.07	178	3.58	3.28–3.87	77		253	
Pain (VAS 0–100 mm)	41	37–45	186	35	29–41	83		267	
Sleep Disturbance (VAS 0–100 mm)	27	23–31	166	22	16–27	69		233	
Fatigue (VAS 0–100 mm)	40	36–44	167	30	25–36	70	2.58	235	< 0.05
Mental Health (SF-36 score 0–100)	74	71–77	182	80	77–84	80	–2.76	178*	< 0.01*
Activity Limitation (HAQ score 0–3)	0.73	0.65–0.81	185	0.44	0.35–0.54	83	4.56	201*	< 0.001*
M24									
Disease Activity (DAS-28 score)	3.70	3.50–3.91	171	3.52	3.19–3.85	75		244	
Pain (VAS 0–100 mm)	37	33–40	185	34	28–39	80		263	
Sleep Disturbance (VAS 0–100 mm)	27	23–31	158	23	17–29	65		221	
Fatigue (VAS 0–100 mm)	39	34–43	158	35	28–42	65		221	
Mental Health (SF-36 score 0–100)	75	72–78	178	79	74–83	74		250	
Activity Limitation (HAQ score 0–3)	0.74	0.65–0.82	181	0.51	0.39–0.62	80	3.02	259	< 0.01
M36									
Disease Activity (DAS-28 score)	3.61	3.38–3.83	153	3.63	3.30–3.95	71		222	
Pain (VAS 0–100 mm)	36	32–40	177	35	29–40	79		254	
Sleep disturbance (VAS 0–100 mm)	25	21–30	154	24	17–30	63		215	
Fatigue (VAS 0–100 mm)	40	36–45	153	31	25–38	64	2.16	215	< 0.05
Mental Health (SF-36 score 0–100)	74	71–77	170	80	76–84	71	–2.00	239	< 0.05
Activity Limitation (HAQ score 0–3)	0.78	0.69–0.86	178	0.41	0.31–0.51	78	5.50	188*	< 0.001*

*Corrections made for unequal variances.

DAS-28: 28-joint count Disease Activity Score; HAQ: health assessment questionnaire; SF-36: 36-item short form health survey; VAS: visual analogue scale.

tween repeated measures. Correlations were calculated with Pearson's correlation coefficients and the consistencies of correlations were examined with the Fisher *r* to *z* transformation. Principal component analysis (PCA) with direct oblimin rotation was performed for each follow-up for women and men separately to identify underlying components in variables representing disease activity and the studied aspects of disability. Significant loadings for principal components were calculated according to Stevens (33). The PCA was based on scree test, Joliffe's criterion of eigenvalues > 0.7, and that the components should permit a reasonable interpretation from a clinical perspective. Multiple linear regression analysis (MLR) was used to explain fatigue by using age at inclusion together with the components identified with the PCA.

p-values < 0.05 were reported if otherwise not specified. All statistics were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 15.0.

Ethics

All patients gave written informed consent to participate. The local ethics committees of the participating units approved the study.

RESULTS

Differences between women and men

At M12 and M36 women reported more fatigue and lower mental health than men, as shown in Table I. To examine the influence of age, the explained variances in fatigue had been analysed and found to be 1% for men and < 0.01% for women; as reported in Table II, the correlations between age and fatigue were small.

Women reported significantly more activity limitation than men at all follow-ups (Table I).

Differences over time

When comparing each variable, at M12 with M24, and M24 with M36, respectively, there were no significant differences, either in women or in men. In women there were no significant differences in correlations between M12 and M24 vs correlations between M24 and M36 (Tables II and III). In men, there was a significantly higher correlation for activity limitation between M12 and M24 vs between M24 and M36, $z = 2.64$, $p < 0.01$ (Tables II and III). In men, there was also a significantly lower correlation for sleep disturbances between M12 and M24 vs between M24 and M36, $z = 2.49$, $p < 0.05$.

Identification of underlying components

In women, the PCA resulted in 2 components. Similar components were revealed for all 3 follow-ups. The first component explained most of the variance. It included disease activity, activity limitation, and pain at all follow-ups (Table IV). Also, sleep disturbance explained this component, but to a large extent it shared the amount of explained variance with the former variables. The second component, which explained a smaller part of the variance, included mental health and sleep disturbance, i.e. high values of mental health in combination with low values of sleep disturbances or vice versa (Table IV).

In men, the PCA revealed similar results as in women, i.e. 2 components at all 3 follow-ups (Table V). The first component included disease activity, activity limitation and pain. The second component included mental health and sleep disturbance. However, there were some differences compared with

Table II. Correlations between fatigue, disease activity, different disability variables, and age at inclusion, at 12 months (M12), at 24 months (M24), and at 36 months after inclusion (M36) for women (upper right) and men (lower left)

Men \ Women	Disease Activity DAS-28 score			Activity Limitation HAQ score 0–3			Pain VAS 0–100 mm			Mental Health SF-36 score 0–100			Sleep disturbance VAS 0–100 mm			Fatigue VAS 0–100 mm			Age at inclusion years		
	M12	M24	M36	M12	M24	M36	M12	M24	M36	M12	M24	M36	M12	M24	M36	M12	M24	M36	M12	M24	M36
Disease Activity, DAS-28 score				0.52***	0.57***	0.55***	0.58***	0.58***	0.58***	–0.28***	–0.34***	–0.34***	0.41***	0.38***	0.41***	0.29***	0.45***	0.41***	0.17*	0.16*	0.18*
Activity Limitation, HAQ, 0–3	0.43***	0.54***	0.28*				0.57***	0.64***	0.56***	–0.35***	–0.42***	–0.31***	0.57***	0.50***	0.44***	0.42***	0.51***	0.49***	0.26***	0.30***	0.36***
Pain, VAS 0–100 mm	0.46***	0.48***	0.27*	0.54***	0.53***	0.38***				–0.43***	–0.46***	–0.34***	0.52***	0.50***	0.41***	0.53***	0.58***	0.42***	0.09	0.11	0.14
Mental Health, SF-36 score 0–100	–0.11	–0.25*	–0.13	–0.23*	–0.37**	–0.37**	–0.32**	–0.34**	–0.38**				–0.40***	–0.55***	–0.47***	–0.34***	–0.48***	–0.46***	–0.09	–0.01	–0.07
Sleep disturbance, VAS 0–100 mm	0.26*	0.04	0.26	0.35**	0.29*	0.37**	0.56***	0.20	0.40**	–0.30*	–0.29*	–0.34*				0.61***	0.61***	0.61***	0.19*	0.14	0.15
Fatigue, VAS 0–100 mm	0.18	0.33*	0.24	0.33*	0.45***	0.27*	0.52***	0.43***	0.50***	–0.40***	–0.30*	–0.44***	0.52*	0.31*	0.47***				–0.05	0.07	0.06
Age at inclusion, years	–0.09	–0.20	–0.08	0.02	0.04	0.01	–0.01	–0.08	–0.12	0.08	–0.08	0.04	–0.06	0.13	0.03	–0.18	–0.07	–0.21			

*$p<0.05$, **$p<0.01$, ***$p<0.0001$.
DAS-28: 28-joint count Disease Activity Score; HAQ: health assessment questionnaire; SF-36: 36-item short form health survey; VAS: visual analogue scale.

the results in women; with respect to the first component at M36, activity limitation and pain had no significant contribution, and sleep disturbance had no significant contribution at any follow-up. With respect to the second component, mental health had no significant influence at M24, and pain had some influence at M36.

Explained variance

In women, the components from the PCA and age at inclusion explained between one-third (M12) and one-half of the variance (M24 and M36) in fatigue, according to the MLR analysis (Table VI). When using the components from the PCA at the follow-up one year earlier as predictors together with age at inclusion, the variance in fatigue at M24 and M36 was explained by approximately one-fourth. When using components from the PCA at M12 as predictors together with age at inclusion, the variance in fatigue at M36 was explained by approximately one-sixth.

At M12, the first component had a greater influence on the prediction of fatigue than the second component, but at M24 and M36 the second component had a greater influence than the first. Age at inclusion had a significant influence on the prediction of fatigue only at M36 (and when using data from all 3 follow-ups simultaneously).

In men, the components from the PCA together with age at inclusion explained almost between one-third (M12 and M24) and one-half of the variance in fatigue (M36) (Table VI). When using the components from the PCA at the follow-up one year earlier as predictors together with age at inclusion, the variance in fatigue at M24 and M36 was explained by approximately one-tenth. When using the components from the PCA at the M12 as predictors together with age at inclusion, the variance in fatigue at M36 was explained by approximately one-fourth.

At M12, the second component had a greater influence on prediction of fatigue than the first component, but at M24, the first component had a greater influence on prediction of fatigue than the second component. At M36, the first component still had the greatest influence on prediction of fatigue, and age at inclusion was a significant predictor.

DISCUSSION

The results of this study of fatigue in early RA included factors chosen to reflect disease activity, different aspects of body function (pain, sleep disturbance, fatigue, and mental health), activity limitation, and personal factors in terms of age and sex (5, 6). There were considerably more women than men, reflecting the typical sex-related incidence of RA, and the women were somewhat younger than the men. All were included in an early intervention programme and in many patients most variables had been improved before this specific study period, i.e. compared with the time of inclusion in the programme, but they were still affected by the disease as reported previously (34).

Compared with men, women reported somewhat more fatigue, activity limitation, and lower mental health through the

Table III. *Consistencies of relations between fatigue vs disease activity and disability aspects between 12 months (M12) vs 24 months after inclusion (M24) and between 24 months vs 36 months after inclusion (M36), given as correlations (R) between M12 and M24 (M12/M24) and correlations between M24 and M36 (M24/M36), for women and men, respectively*

	Women		Men	
Variables	M12/M24 *R* (*n*)	M24/M36 *R* (*n*)	M12/M24 *R* (*n*)	M24/M36 *R* (*n*)
Disease Activity, DAS-28 score	0.54*** (162)	0.57*** (138)	0.40*** (69)	0.48*** (64)
Pain, VAS 0–100 mm	0.54*** (182)	0.45*** (174)	0.45*** (80)	0.40*** (77)
Sleep disturbance, VAS 0–100 mm	0.67*** (145)	0.63*** (140)	0.32*** (54)	0.68*** (53)
Fatigue, VAS 0–100 mm	0.66*** (145)	0.66*** (139)	0.75** (55)	0.55*** (54)
Mental Health, score 0–100	0.64*** (171)	0.59*** (162)	0.36** (72)	0.43*** (66)
Activity Limitation, HAQ score 0–3	0.79*** (177)	0.78*** (173)	0.73***(79)	0.46*** (76)

*$p<0.05$; **$p<0.01$; ***$p<0.001$.
DAS-28: 28-joint count Disease Activity Score; HAQ: health assessment questionnaire; SF-36: 36-item short form health survey; VAS: visual analogue scale.

3 follow-ups of the present study, although the difference was not statistically significant regarding fatigue and mental health at the second follow-up. The finding that the differences with respect to fatigue were not consistently significant through the consecutive measurements may reflect a questionable clinical significance, and is in accordance with the variation of conclusions in the literature about differences between women and men (14, 15, 19, 21). Although the women were somewhat younger than the men, the correlations between age and fatigue were small (Table II) and therefore age was not a likely explanation for the difference with regard to fatigue.

Our results regarding more activity limitation in women tally with other studies, and may be partly due to the lower grip force in women as a group (4). The reported levels of mental health in our groups were similar to the levels of mental health reported by patients with a longer duration of RA and a larger proportion of women in a recent Norwegian study by Odegård et al. (35), and also similar to the levels of a Swedish reference population (34). In American patients with early RA, as well as in American general population norms, considerably lower levels of mental health have been reported (36). Compared with such differences, the difference in mental health between women and men in our study was very small, and the clinical significance is questionable.

Regarding all disease and disability variables, there were no significant differences between the 3 follow-ups, in women or men. The absence of any signs of disease progress with respect to these variables, in the group as a whole, may be due to the

Table IV. *Principal components (C1 and C2) from principal component analysis (PCA) at 12 months (M12), 24 months (M24), and 36 months (M36) after inclusion for women. High indicates high relevance for variable to the component (significant loading in pattern matrix). Partial indicates partial relevance for variable to the component (significant loading in structure matrix but not in pattern matrix). Explained variance is the variance explained for each component and total explained variance is the altogether explained variance. Only significant loadings are presented*

	M12 ($n=151$)			M24 ($n=137$)			M36 ($n=122$)		
Relevance	Variable	Pat	Str	Variable	Pat	Str	Variable	Pat	Str
C1									
High	Disease Activity	0.94	0.85	Disease Activity	0.98	0.90	Disease Activity	0.83	0.82
	Activity Limitation	0.77	0.83	Activity Limitation	0.70	0.82	Activity Limitation	0.88	0.85
	Pain	0.79	0.84	Pain	0.68	0.82	Pain	0.77	0.82
	Sleep Disturbance	0.50	0.68						
Partial				Sleep Disturbance		0.48	Sleep Disturbance		0.54
				Mental Health		–0.46			
Explained variance, %	59			61			56		
C2									
High	Mental Health	0.94	0.94	Mental Health	0.88	0.88	Mental Health	0.94	0.90
	Sleep Disturbance	–0.44	–0.64	Sleep Disturbance	–0.84	–0.86	Sleep Disturbance	–0.73	–0.82
Partial	Activity Limitation		–0.44	Activity Limitation		–0.60	Disease Activity		–0.43
	Pain		–0.49	Pain		–0.61	Pain		–0.49
Explained variance, %	15			15			16		
Total explained variance, %	74			76			71		

Note: Pattern matrix indicates each variable's unique contribution to the component and the structure matrix indicates each variable's total relation to the component.
Pat: loading from pattern matrix; Str: loading from structure matrix; Disease Activity, DAS-28: 28-joint count Disease Activity Score; Activity Limitation, HAQ: Health Assessment Questionnaire; Mental Health, SF-36: 36-item short form health survey; Pain and Sleep Disturbance, VAS: visual analogue scale.

Table V. *Principal components (C1 and C2) at 12 months (M12), 24 months (M24), and 36 months (M36) after inclusion for men. High indicates high relevance for variable to the component (significant loading in pattern matrix). Partial indicates partial relevance for variable to the component (significant loading in structure matrix but not in pattern matrix). Explained variance is the variance explained for each component and total explained variance is the altogether explained variance. Only significant loadings are presented*

	M12 (n=63)			M24 (n=53)			M36 (n=48)		
Relevance	Variable	Pat	Str	Variable	Pat	Str	Variable	Pat	Str
C1									
High	Disease Activity	0.81	0.77	Disease Activity	0.91	0.86	Disease Activity	0.95	0.93
	Activity Limitation	0.78	0.78	Activity Limitation	0.79	0.72			
	Pain	0.75	0.82	Pain	0.67	0.78			
Partial									
Explained variance, %	45			46			46		
C2									
High	Mental Health	0.92	0.90	Sleep Disturbance	0.96	0.95	Mental Health	–0.89	–0.83
							Sleep Disturbance	0.68	0.72
							Pain	0.68	0.70
Partial	Sleep Disturbance		–0.63						
Explained variance, %	26			20			17		
Total explained variance, %	70			66			63		

Note: Pattern matrix indicates each variable's unique contribution to the component and the structure matrix indicates each variable's total relation to the component.

Pat: loading from pattern matrix; Str: loading from structure matrix; Disease Activity, DAS-28: 28-joint count Disease Activity Score; Activity Limitation, HAQ: health assessment questionnaire; Mental Health, SF-36: 36-item short form health survey; Pain and Sleep Disturbance, VAS: visual analogue scale.

early clinical intervention programme. However, the interventions were individually based, complex, and modified according to repeated clinical assessments, and the aim of this study was not to evaluate the effect of these interventions.

According to the results of the PCA in women, the first component included disease activity, activity limitation and pain. Although sleep disturbance had some influence on this component, it shared a large part of explained variance with the former variables. This component explained most of the variance, and in this discussion it is tentatively called *physical disability*. The second component included mental health and sleep disturbance, representing high values of mental health in combination with low values of sleep disturbance, and the reverse. This component explained a smaller part of the variance, and in this discussion it is tentatively called *mental aspects*. The results of the PCA in men were similar to the results in women, although there were some differences. Paying attention to the similarities, the components may tentatively be interpreted in the same terms as in women, i.e. *physical disability* and *mental aspects*. These interpretations of the PCA make sense in relation to a notion that RA is a pathologically well-defined somatic disease with a typical pattern of physical manifestations of varying magnitudes (24), and that the mental aspects of this may vary partly depending on psychosocial mechanisms that are not specific for the disease process, but more dependent on contextual factors (5).

Table VI. *Multiple Linear Regression Analysis with beta-coefficients at 12 months (M12), 24 months (M24), and 36 months after inclusion (M36) respectively, with fatigue as criterion and component 1 and 2 (C1 and C2) together with age at inclusion as predictors. R^2 is explained variance in criterion from predictors*

	Women			Men		
Predictor	M12	M24	M36	M12	M24	M36
M12						
C1	0.38	0.29	0.29	0.28		0.51
C2	–0.31	–0.25	–0.21	–0.44	–0.34	
Age						
R^2	0.34	0.22	0.17	0.34	0.11	0.26
M24						
C1		0.33			0.41	
C2		–0.48	–0.52		0.28	
Age						–0.30
R^2		0.50	0.27		0.30	0.09
M36						
C1			0.34			0.62
C2			–0.45			
Age			–0.17			–0.30
R^2			0.46			0.47

The interpretation of the components is, of course, somewhat subjective, but it is possible to compare with the descriptions of the data in Table IV and V. Like most interpretations, the interpretation of results from a PCA is not easy and not totally objective, and this may be regarded as a methodological disadvantage. However, if the theoretical situation in disability research (5, 20, 37) is taken into consideration, the interpretive part may also be regarded as an important advantage because it may contribute to reflections on, for example, conceptual issues. Although an extensive discussion about the dependency on underlying concepts is beyond the scope of this paper, it is not reasonable to exclude any such reflections from the interpretation of co-variation among the studied variables. For example, if the variables that were tentatively called physical disability in our interpretation, i.e. disease activity, pain, and activity limitation, were analysed conceptually, it is possible that a common denominator would be, for example, painful joints. However, at the same time they could be said to reflect

different aspects, dimensions, or levels of analysis, such as symptoms of disease, body function, and activity. Similarly, it is possible that a common denominator in the definitions of the variables that were tentatively interpreted in terms of mental aspects, i.e. mental health and sleep disturbance, would be, for example, worry. At the same time, these variables could be said to reflect different levels of analysis, such as mental body functions and sleeping in the sense of an "activity" aspect, i.e. something that people do.

According to the results of MLR in women as well as in men, the components *physical disability* and *mental aspects* together explained a substantial part of the variance in fatigue through the 3 follow-ups. Our findings tally partly with the results of Pollard et al. (19), but their conclusion that the association between fatigue and disease activity is only secondary is not supported by our analysis, probably because we first performed a PCA instead of entering the set of inter-related variables directly into the MLR, to avoid artefacts that have been discussed by Huyser et al. (21). Thus, we suggest that disease activity *is* among those factors closely related to fatigue, and this conclusion is in accordance with the results of the intervention part of the study reported by Pollard et al. (19), that treatment with anti-TNF agents results in improvements in disease activity *and* fatigue.

Our results support that fatigue is closely related to physical aspects of disability, such as pain and activity limitation. According to qualitative interviews by Tack (9), patients with RA experience that constant pain as well as different activities are contributing causes of fatigue, but also that fatigue is an important cause of activity limitation. According to a review by Fishbain et al. (18), chronic pain is fatiguing in a number of different diagnoses and sleep problems are commonly found in patients with chronic pain.

Our results also support that fatigue is closely related to mental aspects, which may be a mental reaction to the physical disability. In addition to conceptions of physical causes, the patients interviewed by Tack (9) also felt that variations in fatigue were related to emotional stress. Huyser et al. (21) also concluded that fatigue is related to psychosocial variables, apart from pain and the disease activity *per se*. In addition to the possible influence from a prior affective disorder (38), it is possible that patients with RA get mental health problems as a result of a complex interaction of their pain (39), activity limitations and participation restrictions, personal factors such as low self-efficacy and inadequate coping strategies, and environmental factors, such as lack of social support (21).

To a fairly great extent, the patterns of co-variation between fatigue and the studied variables seem to be consistent, because similar combinations of components explained similar percentages, i.e. 30–50%, of variation according to the MLR at the 1, 2, and 3 year follow-ups. In addition to methodological explanations of the differences in the patterns of co-variation between the years in the group of men with regard to different measures assumed to explain fatigue, it is difficult to exclude the possibility of shifts in the conditions for different disabling mechanisms (20). As shown in Table III, and the results of the Fisher r to z transformation, e.g. sleep disturbance in men, was fairly consistent between M24 and M36 but less consistent between M12 and M24. Also, as shown by the variation of the beta-coefficients in Table VI, in women the component physical disability was the more important predictor than the component mental aspects at M12 (0.38 compared with 0.31), but less important at M24 and M36, while the reverse was seen in men. A shift in disabling mechanisms may be influenced by contextual factors, such as assistive technology, social support, attitudes and financial assets (5, 20, 36). In analogy with this, the different patterns of co-variation among women compared with men could partly be due to different disabling mechanisms, which may contribute to the greater diversity found in the group of men, as expressed by the SD. Also, these differences may, of course, partly be due to methodological factors, such as differences in the sample size.

To measure fatigue, we used a one-dimensional VAS. This scale is commonly used in studies of fatigue in RA and is considered to be reasonably valid (16). The validity of the variable sleep disturbance may be questioned, but we found it reasonable to include a self-reported variable that was in analogy with the variables of pain and fatigue in order to capture the sleep aspect. Although fatigue was studied in relation to a number of factors in order to reflect different aspects of the ICF model (5, 6), environmental aspects were not included and only a few personal factors were studied. In further studies of fatigue it would be valuable to include more contextual aspects, such as personal and environmental factors. Measurements using VAS may be regarded as ordinal and therefore non-parametric, but with such restrictive assumptions there would not be any easy alternative in order to approach the studied problem. Our primary aim was to analyse whether there were differences between women and men with regard to the reported level of fatigue, and to explore the strength of the relations between fatigue and disease activity, pain, sleep disturbance, mental health, and activity limitation. This could have been done with one set of cross-sectional data, but a secondary aim was to explore the consistency of findings in such cross-sectional data in early RA and therefore we used 3 sets. Although these sets of data were longitudinal, the study did not focus on the overall longitudinal pattern because it was not possible to control for interventions, and it was not a part of the aim to analyse causation or to evaluate interventions. Of course, the use of a PCA before the MLR is complicated, but this approach provides a possibility to capture the combined relations between fatigue and the related variables and with consideration to the discussed conceptual issues it may have important advantages compared with more formal and straightforward statistical procedures.

Clinically, it is very important to address fatigue among other outcome aspects (12), and early interventions are now generally recommended in RA. Because there are no suitable direct interventions on fatigue, it is useful to know what aspects are related to fatigue in early RA and our findings may support clinical reasoning about interventions. This study does not permit any conclusions about causal directions; the findings on statistical relationships have to be related to clinical conceptions about causation: When disease activity can be

significantly reduced by pharmacological treatment, this may have a positive effect on pain, mental health, sleep, activity *and* fatigue. Specific treatment with respect to the mentioned disability aspects that are related to fatigue is also a clinically reasonable strategy.

In the perspective of basic research, it would be useful if further studies could clarify causal mechanisms related to fatigue. In future applied and integrative rehabilitation studies (40), it would be interesting to clarify how fatigue and other variables, such as pain and contextual factors, contribute to work disability, which is also an important problem in early RA.

In conclusion, women report more fatigue than men, but the clinical importance of this is debatable because the difference is small and not consistently significant. Fatigue in early RA is closely and rather consistently related to disease activity, pain and activity limitation, and also to mental health and sleep disturbance. Although the causal directions have not been studied, intervention strategies that target the related factors are clinically reasonable.

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