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Effects of psychosocial factors on monitoring treatment effect in newly diagnosed rheumatoid arthritis patients over time: response data from the tREACH study

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Objectives: To investigate whether, apart from effects of patient- and disease-related factors, psychosocial factors have additional effects on disease activity; and which factors are most influential during the first year of treatment in early rheumatoid arthritis (RA).
Method: The study assessed 15 month follow-up data from patients in tREACH, a randomized clinical trial comparing initial triple disease-modifying anti-rheumatic drug therapy to methotrexate monotherapy, with glucocorticoid bridging in both groups. Patients were evaluated every 3 months and treated to target. Associations between Disease Activity Score (DAS) at 3, 9, and 15 months and psychosocial factors (anxiety, depression, fatigue, and coping with pain) at the previous visit were assessed by multivariable linear regression correcting for demographic, clinical, and treatment-related factors.
Results: At 3, 9, and 15 months of follow-up, 265, 251, and 162 patients, respectively, were available for analysis. Baseline anxiety and coping with pain were associated with DAS at 3 months; coping with pain at 6 months was associated with DAS at 9 months, and fatigue at 12 months with DAS at 15 months. Psychosocial factors were moderately correlated. Effects on DAS were mainly due to tender joint count and global health.
Conclusion: Psychosocial factors have additional effects on DAS throughout the first year of treatment in early RA. A change was observed from anxiety and coping with pain at baseline being associated with subsequent DAS towards fatigue being associated with subsequent DAS at 12 months. Owing to the explorative nature of this study, more research is needed to confirm this pattern.

Rheumatoid arthritis (RA) is a common autoimmune disease and is associated with progressive disability, early death, and socio-economic costs (1). Disease progression can be tackled by early treatment with disease-modifying anti-rheumatic drugs (DMARDs), using tightly controlled and treat-to-target strategies (2, 3). This target has been proposed in guidelines as remission or low disease activity, which is commonly measured in clinical practice by composite scores such as the Disease Activity Score (DAS) and the Disease Activity Score based on 28-joint count (DAS28) (4). Recently published studies show that with this regimen a response rate of 40–80% can be reached within 1 year (5, 6). Several patient and disease characteristics, such as baseline disease activity (7, 8), age (7, 9), and gender (7–9), have been reported that may explain part of the variability in response rates. However, a large part of the variability remains unexplained, suggesting that other, unidentified, factors may be at play as well. Recent interest has been directed towards the influence of psychosocial factors. Several studies have reported significant associations between baseline levels of anxiety and/or depression and subsequent DAS or DAS components (10–12). However, the effects of psychosocial factors after treatment has been initiated on disease activity have not been extensively studied. Knowing and understanding the effect of psychosocial factors underlying disease activity and treatment response could provide important information for selection of therapy, evaluation of response, and even targeted psychological interventions aimed at optimizing patient outcome (13).

In this study, we aimed to answer the following questions. (i) Is there, apart from effects of patient- and

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disease-related factors, an additional effect of psychosocial factors on the disease activity during the first year of treatment in an early RA population? (ii) Which compounds of psychosocial factors have the most influence during the disease course?

Method

Study population

Fifteen-month follow-up data were used from the tREACH cohort, for which a detailed description of the inclusion criteria and protocol can be found in the original tREACH paper (6). In brief, patients with early arthritis (duration of complaints < 1 year) and a high risk of developing persistent arthritis [score > 6 points on the Visser model (14)] were eligible. Of the included patients, 97% fulfilled the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria for RA (4). Patients were randomized to the following induction treatment strategies: triple DMARD therapy [iTDT; methotrexate (MTX) 25 mg/week, sulphasalazine 2000 mg/day, and hydroxychloroquine 400 mg/day] or MTX monotherapy 25 mg/week (iMM). Both groups received bridging therapy with glucocorticoids (GCs; triamcinolone acetonide 80 mg or methylprednisolone 120 mg once by intramuscular injection or oral prednisone 15 mg for 4 weeks, thereafter tapered by 5 mg/week). Patients were evaluated every 3 months. In cases where the DAS was > 2.4, patients were switched to a tumour necrosis factor blocker combined with MTX 25 mg/week. If sustained remission (DAS < 1.6 at two consecutive visits) was achieved, medication was tapered according to protocol. Detailed information on the medication scheme can be found in the original tREACH paper (6).

This study was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam, The Netherlands.

Outcomes

Outcomes were the DAS at 3, 9, and 15 months of follow-up.

Psychosocial factors

Psychosocial factors, measured at baseline and 6 and 12 months of follow-up, included coping with pain, anxiety and depression, and fatigue, as explained in more detail below.

Coping with pain. Coping with pain was measured by the Coping with Rheumatic Stressors (CORS) questionnaire. The list contains eight questions about coping with pain (Cronbach's alpha 0.88). Scores range from 8 to 40 (15).

Anxiety and depression. The Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety and depression. The scores for anxiety and depression range from 0 to 21, with higher scores indicating symptoms related to more anxiety or depression (16).

Fatigue. Fatigue was assessed using the Fatigue Assessment Scale (FAS). Questions were asked about the patient's fatigue status. The score ranges from 10 to 50, with higher scores indicating higher levels of fatigue (17).

Demographic, disease-related, and treatment-related factors

Age, gender, rheumatoid factor (RF), and anti-citrullinated protein (ACPA) status were assessed at baseline. For this study, initial treatment strategy was included as a binary variable, indicating MTX monotherapy with GC bridging (coded 1) versus initial triple DMARD therapy with either oral or intramuscular GC bridging (coded 0). At follow-up visits, medication increase was defined as a dose increase or a switch to other medication. Medication decrease was defined as a dose decrease or discontinuation of medication. Medication increase and decrease were also included as binary variables.

Statistical analyses

Missing data. In those patients with an available outcome DAS, missing values in covariates at the previous visit (see supplementary Table S1) were completed using multiple imputation with chained equations (mi impute chained procedure in STATA). Given that the largest missing rate observed was 42.3% (supplementary Table S1), a number of m = 50 imputations was chosen, taking into consideration the rule of thumb that the number of imputations should at least be equal to the percentage of incomplete cases (18). To avoid bias, imputation models were constructed such that all variables used in the analysis models were included in the imputation models (18). Before imputation, continuous variables were transformed to normality using the 'nscore' package for STATA (19) and transformed back to their original scale afterwards, ensuring that imputed values could not lie outside the observed data range (19). The complete specification of imputation models can be found in Supplementary file S2.

Analyses. Multivariable linear regression analyses were performed for psychosocial factors, measured at baseline and 6 and 12 months of follow-up, on outcome DAS at 3, 9, and 15 months of follow-up, respectively, and correcting for demographic, disease-related, and treatment-related factors.

First, DAS was regressed against each individual psychosocial factor, controlling for DAS and medication change at the previous visit and the baseline factors age, gender, RF, and ACPA positivity. Then, a full

model was built containing all four psychosocial factors together and controlling for the same factors. Backward elimination was performed on the full model until remaining psychosocial factors were significant. Statistical analyses were performed using STATA 14.1 (StataCorp, College Station, TX, USA) and p values < 0.05 were considered statistically significant.

Results

In total, 281 patients were available for analysis, 161 of whom had outcome DAS available at all three visits (completers). Overall, the mean age was 53 years and 190 (68%) were female (Table 1). Mean baseline DAS was 3.36 and 95% fulfilled the ACR/EULAR 2010 criteria for RA (6) (Table 1). Completers and non-completers were similar with respect to baseline characteristics, except for a slightly higher percentage of completers being RF positive and fulfilling the ACR/EULAR 1987 criteria (Table 1).

Association after 3 months of treatment

Analyses of each psychosocial factor individually, correcting for age, gender, RF, ACPA, and baseline DAS, revealed that higher levels of anxiety, coping with pain, and depression were associated with a higher DAS at 3 months of follow-up. After applying backward elimination on the full model, anxiety and coping with pain were independent predictors for DAS at 3 months of follow-up. In sensitivity analysis by bootstrap samples, anxiety and coping with pain were selected in 65.3% and 56.7% of samples, whereas depression and fatigue were selected in < 15% of samples (Table 2).

Association after 9 months of treatment

In the per-factor analysis of psychosocial factors, correcting for age, gender, RF, ACPA, and DAS at 6 months, coping with pain was associated with DAS at 9 months and fatigue showed a borderline significant association. After backward elimination, coping with pain remained as a significant predictor for DAS at 9 months of follow-up. In sensitivity analyses on bootstrap samples, coping with pain was selected in 59.2% of samples and fatigue in 20.4% of samples.

Association after 15 months of treatment

Per-factor analysis showed that only fatigue was significantly associated with DAS at 15 months when correcting for age, gender, RF, ACPA, and DAS at 12 months. This was also the case in the backward elimination model. In sensitivity analyses on bootstrap samples, fatigue was

Table 1. Baseline characteristics.

Characteristics	All patients (n = 281)	Completers (outcome DAS available at 3, 9, and 15 months) (n = 161)	Non-completers (outcome DAS missing at 3, 9, or 15 months) (n = 120)	p*
Demographic				
Age (years)	53 (14)	53 (14)	53 (14)	0.981
Gender (female)	190 (68)	104 (65)	86 (72)	0.210
Disease-related				
Duration of complaints (days)	166 ± 91	168 ± 87	164 ± 97	0.662
RF-positive	228 (81)	138 (86)	90 (75)	0.023
ACPA-positive	226 (80)	133 (83)	93 (78)	0.286
Fulfilling ACR/EULAR 1987 criteria	189 (67)	118 (73)	71 (59)	0.013
Fulfilling ACR/EULAR 2010 criteria	267 (95)	154 (96)	113 (94)	0.571
DAS	3.36 ± 0.96	3.39 ± 0.97	3.33 ± 0.95	0.648
HAQ	1.00 ± 0.66	0.97 ± 0.65	1.03 ± 0.67	0.496
tSvHs	0 (0–0)	0 (0–0)	0 (0–0)	0.266†
Anxiety (HADS)	5.8 ± 3.7	5.8 ± 3.9	5.8 ± 3.5	0.861
Depression (HADS)	4.6 ± 3.4	4.5 ± 3.4	4.6 ± 3.4	0.843
Fatigue (FAS)	22.2 ± 7.0	22.6 ± 7.3	22.0 ± 6.8	0.542
Coping with pain (CORS)	15.5 ± 5.2	16.2 ± 5.2	15.0 ± 5.1	0.058

Data are shown as n (%), mean ± sd, or median (interquartile range).
*Differences between completers and non-completers were tested. Student's t-test and Pearson's chi-squared test were used as appropriate, unless specified otherwise.
†Wilcoxon rank-sum test.
RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; tSvHs, total Sharp van der Heijde score; HADS, Hospital Anxiety and Depression Scale; FAS, Fatigue Assessment Scale; CORS, Coping with Rheumatic Stressors.

Table 2. Multivariable linear regression analysis of psychosocial factors at baseline and 6 and 12 months on Disease Activity Score (DAS) at 3, 9, and 15 months, respectively.

	Multivariable, per factor			Multivariable, full			Multivariable, after backward elimination			
	Beta	p	95% CI	Beta	p	95% CI	Beta	p	95% CI	%*
DAS 3 months (n = 265)										
Anxiety (T0)	**0.043**	**0.005**	**0.013 to 0.073**	0.037	0.050	−0.000 to 0.075	**0.037**	**0.015**	**0.007 to 0.067**	65.3
Depression (T0)	**0.034**	**0.037**	**0.002 to 0.066**	−0.001	0.963	−0.044 to 0.042				11.4
Fatigue (T0)	0.015	0.070	−0.001 to 0.031	0.001	0.935	−0.189 to 0.020				7.8
Coping with pain (T0)	**0.028**	**0.012**	**0.006 to 0.051**	0.024	0.051	−0.000 to 0.048	**0.024**	**0.036**	**0.002 to 0.046**	56.7
DAS 9 months (n = 251)										
Anxiety (T6)	0.017	0.217	−0.010 to 0.044	0.004	0.822	−0.034 to 0.043				12.3
Depression (T6)	0.023	0.115	−0.006 to 0.052	0.001	0.975	−0.046 to 0.048				12.6
Fatigue (T6)	0.014	0.060	−0.001 to 0.028	0.006	0.602	−0.015 to 0.026				20.4
Coping with pain (T6)	**0.025**	**0.016**	**0.005 to 0.045**	0.021	0.081	−0.003 to 0.044	**0.025**	**0.016**	**0.005 to 0.045**	59.2
DAS 15 months (n = 162)										
Anxiety (T12)	0.012	0.459	−0.020 to 0.043	−0.013	0.525	−0.055 to 0.028				11.6
Depression (T12)	0.028	0.095	−0.005 to 0.060	0.011	0.669	−0.040 to 0.062				18.2
Fatigue (T12)	**0.019**	**0.020**	**0.003 to 0.035**	0.017	0.179	−0.008 to 0.041	**0.019**	**0.020**	**0.003 to 0.035**	51.5
Coping with pain (T12)	0.019	0.102	−0.004 to 0.041	0.007	0.619	−0.019 to 0.033				13.4

All analyses are corrected for age, gender, rheumatoid factor, anti-citrullinated protein antibodies, initial treatment group, medication change at the previous visit, and DAS at the previous visit.
*Selection rate of psychosocial factors after applying backward elimination in bootstrap samples.
The figures in bold type indicate a significant association for the covariate with the outcome.

selected in 51.5% of instances, whereas other psychosocial factors were selected in < 20% of samples.

Correlation between psychosocial factors

Pearson correlations between psychosocial factors for each time-point are shown in supplementary Table S3. In particular, anxiety, depression, and fatigue were highly correlated with each other, with correlation coefficients around 50–70%. Coping with pain shows moderate correlations with the other factors, with correlation coefficients around 25–50%.

Course over time of psychosocial factors

To gain further insight, development over time of psychosocial factors was investigated (supplementary Figure S4). All scores showed significant decreases at 6 and 12 months with respect to baseline scores, except for coping with pain at 6 months.

Associations between psychosocial factor and DAS components

To evaluate which DAS components are associated with psychosocial factors at the previous visit, linear and zero-inflated negative binomial regression models were performed (Table 3). The most significant associations were observed for the subjective components Ritchie Articular Index (RAI) and Global Health (GH). Some significant associations for objective components were also observed: higher levels of baseline coping with pain were associated with both a higher 44-joint swollen joint count (SJC44) and erythrocyte sedimentation rate (ESR) at 3 months, while higher levels of fatigue at 6 months were associated with lower levels of ESR at 9 months (Table 3).

Discussion

In this longitudinal study of RA patients starting with DMARD therapy, we found that psychosocial factors were independently associated with DAS at the next 3 monthly visit during the first year of follow-up. The psychosocial factors associated with DAS changed over time: coping with pain and anxiety influenced the disease activity in the first 3 months, but anxiety no longer appeared to play a role after 9 months of treatment. In the phase where disease activity is low, only fatigue played a role. Although speculative, the change observed may indicate a shift in the relative importance of psychosocial factors over the course of disease in newly diagnosed patients with RA. In the first months after diagnosis, when disease is still active and optimal treatment effect has not yet been achieved, it is imaginable that anxiety and coping with pain play a more pronounced role, especially by affecting the more subjective components of DAS RAI and GH. Later on, when disease is under control and patients have adapted to living with the disease, fatigue could be more in the foreground. However, it should be noted that the

Table 3. Association of psychosocial factors at baseline and 6 and 12 months on Disease Activity Score (DAS) components at 3, 9, and 15 months, respectively, by zero-inflated negative binomial regression or linear regression.

	SJC44*		ln ESR†		RAI*		GH†	
	Beta	p	Beta	p	Beta	p	Beta	p
DAS 3 months (n = 252)								
Anxiety (T0)	0.006	0.723	–0.005	0.752	**0.033**	**0.031**	**1.728**	**<0.001**
Depression (T0)	–0.002	0.895	0.016	0.353	0.008	0.631	**1.687**	**<0.001**
Fatigue (T0)	0.014	0.129	–0.004	0.648	0.008	0.361	**0.726**	**0.001**
Coping with pain (T0)	**0.046**	**<0.001**	**0.030**	**0.008**	0.021	0.055	0.121	0.677
DAS 9 months (n = 214)								
Anxiety (T6)	0.004	0.859	–0.014	0.469	0.012	0.508	**1.689**	**<0.001**
Depression (T6)	–0.020	0.371	–0.024	0.226	0.026	0.159	**2.199**	**<0.001**
Fatigue (T6)	–0.002	0.821	**–0.024**	**0.011**	**0.025**	**0.003**	**1.045**	**<0.001**
Coping with pain (T6)	–0.015	0.379	–0.015	0.275	**0.029**	**0.025**	**0.900**	**0.008**
DAS 15 months (n = 141)								
Anxiety (T12)	0.008	0.817	–0.010	0.636	0.020	0.458	0.499	0.334
Depression (T12)	–0.041	0.247	0.013	0.547	0.041	0.078	0.717	0.172
Fatigue (T12)	0.001	0.952	–0.008	0.494	**0.039**	**0.002**	0.478	0.083
Coping with pain (T12)	0.017	0.462	–0.011	0.514	**0.063**	**<0.001**	–0.158	0.686

All analyses are corrected for age, gender, rheumatoid factor, anti-citrullinated protein antibodies, initial treatment group, medication change at the previous visit, and DAS at the previous visit.
*Zero-inflated negative binomial regression.
†Linear regression.
SJC44, 44-joint swollen joint count; ln, natural logarithm; ESR, erythrocyte sedimentation rate; RAI, Ritchie Articular Index; GH, Global Health.
The figures in bold type indicate a significant association for the covariate with the outcome.

psychosocial factors that we investigated are highly correlated, which is in line with previous studies that found that symptoms of anxiety and depression often co-occur in RA patients (20). Therefore, care should be taken in drawing definite conclusions with respect to the importance of one factor over another, and no definite conclusions of a change in relative importance should be drawn based on the results of this study alone. However, overall, our results do suggest that psychosocial factors in general appear to play an additional role in explaining responses to treatment during the entire first year of follow-up.

Several previous studies have investigated the effects of psychosocial factors on DAS at subsequent visits. In a secondary analysis of a clinical trial in early RA, Matcham et al. (12) found that both baseline and persistent symptoms of depression/anxiety symptoms, measured on a combined scale of the EuroQol 5 Dimensions (EQ-5D), were associated with increased DAS28 scores over the first 2 years of follow-up. This is partly in agreement with our study, in which we found both baseline anxiety and depression scores to be associated with higher DAS at 3 months of follow-up, but not at later time-points (12). Differences may, at least in part, be explained by the use of a different instrument to measure depression/anxiety symptoms and differences in analytical approach (linear mixed model averaging outcome over time) (12).

Previous studies have also looked into which components of the DAS are associated with psychosocial distress. In the COMET trial, significant associations between depression and both subjective (i.e. tender joint count and general health) and objective (i.e. swollen joint count and ESR) components of DAS were observed (10), whereas Matcham et al. only found associations for subjective components of DAS (11, 12). Regarding our own results, most associations are observed for the subjective components (Table 3). In patients with high levels of psychosocial distress, this may lead to overtreatment and higher costs if rheumatologists perform DAS-steered treatment without recognizing that the increased DAS is based on subjective components rather than inflammation. We therefore recommend that rheumatologists be aware of psychosocial distress and its impact on DAS when adjusting therapy.

Several strengths and limitations of this study should be noted. Strong points include the fact that data were used from a prospective randomized clinical trial on early RA patients who were treated to target according to current guidelines (2, 3). Although not powered for this analysis, the sample size appears to be adequate for the scope of this analysis. The number of missing values in predictor variables was small at baseline, but increased at follow-up visits (supplementary Table S1). To increase power and avoid bias in the analysis, we used multiple imputation to complete missing covariates for those patients having an outcome DAS available at the subsequent visit. Nonetheless, the complete case analysis for patients without missing covariates showed similar results (supplementary Table S5). Few studies have assessed

the additional effect of psychosocial factors on DAS and, to our knowledge, no previous studies have assessed them at specific time-points after baseline.

Several limitations should be mentioned as well. By the multiple imputation procedure, we completed missing covariates for those patients having an outcome DAS available at the subsequent visit. However, this does not take into account potential selection bias by patients completely dropping out from the study over time. Although selective dropout cannot be ruled out, patients with complete and incomplete follow-up were similar with respect to most baseline characteristics (Table 1). Furthermore, in a secondary analysis in selected patients with complete follow-up only (supplementary Table S7), except for baseline depression and coping with pain in relation to DAS after 3 months, which could be related to the smaller sample size, all psychosocial factors identified in the main analysis (Table 2) maintained significance.

Data were used from a randomized clinical trial that was not designed for the purpose of these analyses. As the clinical trial setting differs from clinical practice, it cannot be ruled out that by selection bias different effects would have been observed if a similar study were performed in a clinical practice setting. Another potential limitation is the issue of multiple testing. Because of the explorative nature of the study and commonly available solutions such as the Bonferroni method tend to be highly conservative, no formal methods were applied to account for this. Although under the null hypothesis it is still highly unlikely that five out of 12 significant associations (multivariable per-factor analysis, Table 2) would be obtained by chance alone, it cannot be ruled out that some of these were due to chance.

Conclusion

We found that psychosocial factors affect subsequent DAS during the first year of follow-up in patients newly diagnosed with RA. A change in pattern was observed from anxiety and coping with pain being associated with subsequent DAS at baseline towards fatigue being associated with subsequent DAS at 12 months of follow-up. Owing to correlation between psychosocial factors and the explorative nature of this study, more research is needed to confirm this pattern.

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References

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205–19.
2. Singh JA, Saag KG, Bridges SL Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1–26.
3. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.
4. de Jong PH, Hazes JM, van Zeben D, van der Lubbe PA, de Jager MH, de Sonnaville PB, et al. Treatment decisions and related costs differ significantly depending on the choice of a disease activity index in RA, according to 1987 and 2010 classification criteria. Rheumatology (Oxford) 2012;51:1269–77.
5. Bijlsma JW, Welsing PM, Woodworth TG, Middelink LM, Petho-Schramm A, Bernasconi C, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet 2016;388:343–55.
6. de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. Ann Rheum Dis 2014;73:1331–9.
7. Drouin J, Haraoui B. Predictors of clinical response and radiographic progression in patients with rheumatoid arthritis treated with methotrexate monotherapy. J Rheumatol 2010;37:1405–10.
8. Saevarsdottir S, Wallin H, Seddighzadeh M, Ernestam S, Geborek P, Petersson IF, et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 2011;70:469–75.
9. Ma MH, Ibrahim F, Walker D, Hassell A, Choy EH, Kiely PD, et al. Remission in early rheumatoid arthritis: predicting treatment response. J Rheumatol 2012;39:470–5.
10. Overman CL, Bossema ER, van Middendorp H, Wijngaards-de ML, Verstappen SM, Bulder M, et al. The prospective association between psychological distress and disease activity in rheumatoid arthritis: a multilevel regression analysis. Ann Rheum Dis 2012;71:192–7.
11. Matcham F, Ali S, Irving K, Hotopf M, Chalder T. Are depression and anxiety associated with disease activity in rheumatoid arthritis? A prospective study. BMC Musculoskelet Disord 2016;17:155.
12. Matcham F, Norton S, Scott DL, Steer S, Hotopf M. Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. Rheumatology (Oxford) 2016;55:268–78.
13. Santiago T, Geenen R, Jacobs JW, Da Silva JA. Psychological factors associated with response to treatment in rheumatoid arthritis. Curr Pharm Des 2015;21:257–69.
14. Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. Arthritis Rheum 2002;46:357–65.
15. van Lankveld W, Naring G, van der Staak C, van 't Pad Bosh P, van de Putte L. [De ontwikkeling van de CORS. Coping met Reuma Stressoren], in Dutch. Gedrag Gezondheid 1993;21:40–8.
16. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002;52:69–77.
17. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the Fatigue Assessment Scale. J Psychosom Res 2003;54:345–52.

18. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011;30:377–99.
19. Lunt M A guide to imputing missing data with Stata (revision: 1.4) (http://personalpages.manchester.ac.uk/staff/mark.lunt/mi_guide.pdf). Accessed 20 July 2017.
20. Rayner L, Matcham F, Hutton J, Stringer C, Dobson J, Steer S, et al. Embedding integrated mental health assessment and management in general hospital settings: feasibility, acceptability and the prevalence of common mental disorder. Gen Hosp Psychiatry 2014;36:318–24.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Missing values.
Supplementary file S2. Multiple Imputation.
Supplementary Table S3. Pearson correlation coefficients of psychosocial factors at baseline, 6 months and 12 months of follow-up.
Supplementary Figure S4. Mean levels of anxiety, depression, fatigue, and coping with pain over time.
Supplementary Table S5. Multivariable linear regression analysis of psychosocial factors at baseline, 6 and 12 months on DAS at 3, 9, and 15 months, respectively.
Supplementary Table S6. Analysis of multicollinearity.
Supplementary Table S7. Multivariable linear regression analysis of psychosocial factors at baseline, 6 and 12 months on DAS at 3, 9, and 15 months, respectively.

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