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Psychosocial burden predicts sustained remission in early rheumatoid arthritis: unraveling the complex interplay of wellbeing and disease activity

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Abstract

OBJECTIVES To investigate how psychosocial aspects affect the probability of achieving sustained remission in early RA, and to explore the directionality of this relationship.

METHODS Data were analyzed from the randomized controlled CareRA-trial. Sustained remission was defined as continued DAS28-CRP <2.6 from weeks 16 to 104. Patients completed the Short Form 36 (SF-36), Revised Illness Perception Questionnaire (IPQ-R) and Utrecht Coping List (UCL). These psychosocial variables were studied at baseline and week 16 as predictors of sustained remission with logistic regression. Next, subgroups of patients in remission at week 16 were identified by Latent Profile Analysis (LPA) based on these psychosocial indicators. Time to first loss of remission was then compared between groups by Cox-proportional-hazards regression. Finally, directionality of associations between psychosocial indicators and DAS28-CRP was explored with cross-lagged panel models (CLPM).

RESULTS Sustained DAS28-CRP-remission was associated with higher SF-36-scores and less passive coping at baseline, and with higher SF-36-scores and more positive IPQ-R-outcomes at week 16. Among patients in DAS28-CRP-remission at W16 (n=287), two subgroups were identified: a low-psychosocial-burden group (n=231/287) and high-psychosocial-burden group (n=56/287). The low-psychosocial-burden group retained remission longer (HR 0.51 [0.35-0.73]). In the CLPM, temporal relationships between psychosocial wellbeing and DAS28-CRP were complex, bidirectional and disease-phase dependent.

CONCLUSION Suboptimal psychosocial wellbeing and negative illness perceptions predicted lower probability of sustained remission in an early RA cohort. Illness perceptions appeared to become more clinically relevant with time. Finally, one-in-five patients showed worse

psychosocial outcomes despite early remission, and these patients tended to lose remission earlier.

Significance and Innovations:

- Illness perceptions and psychosocial wellbeing during early disease might influence the probability of sustained remission.
- Temporal relationships between psychosocial wellbeing and disease activity appear complex, bidirectional and disease-phase dependent.
- Suboptimal wellbeing despite remission is common and clinically relevant and warrants specific attention from clinicians.
- Illness perceptions need time to evolve beyond the impactful period of diagnosis and treatment initiation.

Clinical outcomes of rheumatoid arthritis (RA) are continually improving, because of treating-to-target and the availability of novel disease-modifying antirheumatic drugs (DMARDs)(1–4). However, even when clinical treatment targets are met, many patients with RA still report ongoing symptoms, including pain and fatigue (5). Crucially, controlling these symptoms and being able to lead a 'normal' life despite their disease appear to be the most important goals for patients (6). It is therefore relevant to consider these unmet patient needs when assessing disease control, and to work towards patient-preferred goals (7). This could be facilitated by using patient-reported outcomes (PROs) to complement the evaluation of disease burden (8). Additionally, PROs like pain and physical function appear to be stronger predictors of remission than traditional prognostic factors such as autoantibodies or radiographic erosions (9,10).

However, while pain, fatigue and physical function are now widely collected as PROs for RA, less attention is often given to mental health and psychosocial wellbeing (11). Research has shown that suboptimal mental health persists in many patients with RA, despite successful treatment (7,12). Additionally, illness perceptions, particularly during early disease, contribute strongly towards adjustment to chronic illness (13). In RA, patients' perceptions about their disease also influence levels of pain and functioning (14,15). Furthermore, personality characteristics and psychological stressors during the early course of RA are known predictors of long-term anxiety and depressed mood (16). Despite this evidence, psychosocial wellbeing and illness perceptions are still rarely assessed in practice or even in clinical trials, and particularly not as specific endpoints informing person-centered interventions (17).

During the Care in Early RA (CareRA) trial, which compared several DMARD-regimens for early RA (18), numerous PROs relating to psychosocial wellbeing were collected. Results showed

that psychosocial functioning after 1 year of treatment was mainly influenced by the initial treatment response (19,20). However, one-in-five patients in CareRA, despite responding well to treatment, continued to report signs of poor wellbeing, again reflecting unmet patient needs (21).

Nonetheless, it is often unclear whether these unmet needs should either be seen as a distinct issue, or as a disease-related complication that could in turn affect clinical disease control. For instance, although a negative association of depression and anxiety with remission has been suggested (22,23), it is less evident whether more general indicators of wellbeing also affect clinical outcomes. A better understanding of the relationship between psychosocial wellbeing, coping, illness perceptions and disease activity, and the directionality of these relations, could help clinicians to distinguish between patient needs that require pharmacological interventions and needs that are better addressed otherwise. Moreover, it remains unclear whether suboptimal psychosocial wellbeing should be intervened upon during the early stages of disease, or if this only later becomes more relevant.

Therefore, we aimed to assess how patients' psychosocial characteristics affect disease activity and remission or vice versa during the early course of RA.

Patients and Methods

Study design and participants

We conducted a post-hoc analysis of the CareRA-trial. CareRA (EudraCT: 2008-007225-39) was a multicenter, prospective, two-year, pragmatic RCT comparing DMARD-regimens for early RA (18). In total, 379 patients were recruited from 13 Belgian rheumatology centers. All participants were diagnosed with RA <1 year ago and were DMARD-naïve at study initiation. Details on the study protocol and main results are published elsewhere (18,24). Briefly, all

treatment arms consisted of methotrexate ± additional csDMARDs or bridging glucocorticoids. The ethics committee of each participating center approved the study protocol and all participants provided written informed consent. This analysis included the entire CareRA-cohort and required no additional ethical approval.

Assessments

Participants were assessed at screening, baseline, week 4, 8, 16, 28, 40, 52, 65, 78, 91 and 104. At screening, demographic characteristics were collected and past or current co-morbidities of depression/anxiety were registered, defined as either a confirmed diagnosis or use of antidepressants. Each following assessment included tender and swollen joint counts, patient's and physician's global assessment of disease activity (PGA/PhGA) on a visual analogue scale (VAS), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). DAS28, CDAI and SDAI were calculated as composite scores (25,26). Moreover, numerous PROs were collected at different times, including pain and fatigue (VAS), the Health Assessment Questionnaire (HAQ), the Revised Illness Perception Questionnaire (IPQ-R) and the Short-Form 36 health survey (SF-36) (27–29). Coping was assessed at baseline and week 16 using the Utrecht Coping List (UCL) (30).

The IPQ-R measures 9 dimensions of illness perception: identity, consequences, timeline acute/chronic, timeline cyclical, treatment control, personal control, emotional representations, illness coherence and causes (28). Higher scores on illness coherence, treatment control and personal control represent a better understanding of RA and stronger beliefs in the ability of treatment or personal interventions to control the disease. Higher scores on emotional representations and consequences indicate stronger perceptions about the negative consequences of RA.

The SF-36 measures 8 dimensions of health divided into 4 physical dimensions (physical function, role physical, bodily pain, and general health; summarized in the physical component score PCS) and 4 mental dimensions (vitality, social functioning, role emotional, and mental health; summarized in the mental component score MCS) (29). Higher scores on SF-36 dimensions (0-100) indicate a better perceived health status.

Finally, the UCL measures seven coping strategies, with higher scores indicating more use of a certain strategy (30).

Outcomes

We aimed to investigate how indicators of psychosocial wellbeing affect the probability of achieving sustained remission in early RA, and additionally, how disease activity and psychosocial factors might interrelate over time. According to this research question, we selected the UCL, the mental health dimensions of the SF-36 and the IPQ-R-dimensions illness coherence, consequences, treatment control, personal control, and emotional representations as the most relevant psychosocial variables. Additionally, depression/anxiety was considered as a possible confounder. At each time point, remission was defined dichotomously as DAS28-CRP <2.6 (31). Sustained remission was defined as a continued state of remission from weeks 16 to 104. As a sensitivity analysis, results were compared for CDAI-remission, SDAI-remission and ACR-EULAR Boolean remission (26,32).

Statistical analysis

Descriptive statistics were reported as means (± SD), medians (± IQR) or proportions as appropriate. First, baseline clinical and demographic characteristics of patients achieving or not achieving sustained remission were compared using a t-test, Mann-Whitney-U-test or Chi-

square test depending on data distribution. Variables that showed statistically significant differences between these groups were explored with multivariate logistic regression predicting sustained remission and adjusted for age, gender, treatment arm and the presence of autoantibodies.

Second, we constructed logistic regression models predicting the odds of sustained remission with the available psychosocial PROs as individual predictors, adjusted for age, gender, treatment arm, autoantibodies, and the two-component DAS28 (2C-DAS28) at the time of assessment. The 2C-DAS28 is a reweighted combination of swollen joint counts and CRP that represents joint inflammation rather than global disease activity (33). By adjusting for 2C-DAS28 instead of the four-component DAS28, we aimed to prevent collinearity between the PGA and other PROs. Similarly, individual regression models included only one of the psychosocial variables at any time. These prediction models were intended as an exploratory step to select, among the many available psychosocial indicators, the most clinically relevant PROs to include in the following analyses (Figure 1). Therefore, no correction for multiple comparisons was applied.

Third, we performed a Latent Profile Analysis (LPA) to identify distinct psychosocial profiles among patients, based on normalized scores on the selected subset of PROs. LPA aims to discover hidden subgroups within observed data based on a set of continuous variables (34). Contrary to distance-based clustering algorithms, LPA models the probability of each patient belonging to a certain profile, which allows for more flexibility while also providing fit statistics. The optimal model and number of profiles were chosen based on Akaike and Bayesian Information Criterion (AIC/BIC), with lower numbers representing better model fit (35). By first selecting a relevant subset of PROs to include, LPA then allowed us to distinguish between patients with specific psychosocial profiles. This method was applied at week 16

specifically to the subgroup of patients who were in remission, to assess if differing psychosocial phenotypes could be found among these patients despite clinical disease control. Next, the clinical impact of such phenotypes was studied by comparing the time to first loss of remission between different profiles identified at week 16. This time-to-event analysis was based on Kaplan-Meier and Cox-proportional hazards regression with profile-membership as the predictor and adjusting for age, gender, treatment arm, and autoantibodies.

Finally, we explored the directionality of associations between the selected psychosocial indicators and DAS28-CRP. To reduce error due to repeated measurement of multiple variables, psychosocial wellbeing was first established as a latent construct loaded upon by the selected psychosocial indicators with confirmatory factor analysis (CFA), and the stability of this construct over time (measurement invariance) was validated (Supplement 1 provides detailed methods) (36). Next, directionality and temporal nature of the association between the psychosocial wellbeing construct and DAS28-CRP was studied with a cross-lagged panel model (CLPM), adjusted for age, gender, treatment arm and autoantibodies. CLPMs can be applied to longitudinal data to estimate directionality of effects between variables at different points in time while adjusting for changes in the variables themselves, which might contribute to stronger causal claims (37).

Missing SF-36-items were first substituted with the respondent's average score on the same subscale's completed items when at least half of the items were answered, in accordance with the questionnaire's manual. Thereafter, missing data were assumed to be missing at random and imputed with multiple imputation (100 imputations, 16% total missingness, imputation by classification and regression trees). Before analysis, imputations were pooled into a single dataset containing the means of imputed values. A p-value <0.05 was considered

as statistically significant for all analyses. Analyses were carried out in R Studio version 1.3.1093, with inclusion of the *mice*, *lavaan*, *tidyLPA* and *survival*-packages.

Results

Patient characteristics

In total, 379 patients with early RA were included in CareRA between January 2009 and May 2013. Among these patients, 322 (85%) completed the two-year study. This post-hoc analysis included all 379 participants after imputation of missing data (Table 1).

Clinical predictors of sustained remission

Sustained DAS28-CRP-remission was achieved by 124/379 (33%) patients. Only 46/379 (12%) patients reached sustained CDAI-remission, and both sustained SDAI-remission and sustained remission based on ACR-EULAR Boolean criteria were attained in only 21/379 (6%) patients. However, although in most cases remission was not sustained until week 104, most patients did achieve DAS28-CRP-remission by week 16 or week 28 (Supplement 2).

Baseline demographic characteristics did not differ between the groups that did or did not achieve sustained DAS28-CRP-remission, except for a lower BMI in the sustained remission group (Table 1). However, patients who achieved sustained remission had, at baseline, a significantly lower DAS28-CRP, lower tender and swollen joint counts, lower PGA and PhGA, less pain and fatigue and lower HAQ. There were no statistically significant differences for CRP, ESR or the presence of depression/anxiety.

In multivariate analyses, BMI no longer predicted sustained remission, while lower baseline DAS28-CRP, tender and swollen joint counts, PGA, PhGA, pain and fatigue and HAQ remained associated with increased odds of sustained remission (Supplement 3).

Psychosocial predictors of sustained remission

In multivariate models, higher baseline scores on all SF-36 mental components were associated with increased odds of sustained remission (Table 2). In addition, the UCL-dimension of passive reacting negatively predicted sustained remission ($p = 0.037$), unlike other coping mechanisms. Finally, illness perceptions at baseline showed no statistically significant association with sustained remission, although a clear positive trend was seen for illness coherence ($p = 0.052$).

At week 16, better scores on all SF-36 mental components were associated with increased odds of sustained remission, with markedly higher odds ratios than at baseline (Table 2). Furthermore, contrary to baseline, more positive illness perceptions on all selected IPQ-R-dimensions at week 16 predicted sustained remission. However, at week 16, coping mechanisms were no longer significantly predictive. Therefore, the UCL was not included in the following analyses, and psychosocial wellbeing was defined in both the LPA and the CLPM by the four mental components of the SF-36 and all 5 available dimensions of the IPQ-R (Supplement 1B).

Psychosocial patient profiles

Figure 2 shows the results of LPA of patients in DAS28-CRP-remission at week 16 (n=287). Optimal model fit was achieved for 2 profiles with equal variances and covariances (Supplement 4). Although the normalized PRO-responses overlapped between profiles, the LPA distinguished between patients with low and high psychosocial burden despite being in remission. The low-psychosocial-burden profile consisted of 231/287 (80%) patients, the high-psychosocial-burden profile of 56/287 (20%) patients. Similar results were obtained

when clustering patients in CDAI-remission. The limited number of patients in SDAI-remission and ACR-EULAR Boolean remission did not allow for efficient clustering. However, when examining patients in low-disease-activity (LDA) (including remission) based on SDAI, results were similar to those for DAS28- and CDAI-remission.

Sustainability of remission by psychosocial profile

Among patients in DAS28-CRP-remission at week 16, the low-psychosocial-burden profile showed a significantly longer time to first loss-of-remission when compared with the high-psychosocial-burden group (HR 0.51 (0.35-0.73), $p < 0.001$) (Figure 3). Similar results were obtained for CDAI-remission (HR 0.54 (0.32-0.89), $p = 0.016$). Time-to-event tables are presented in Supplement 5. For patients in LDA or remission based on SDAI, results were comparable (Supplement 6).

The complexity of psychosocial wellbeing and disease activity

Although the factor structure for the latent construct of psychosocial wellbeing remained robust, factor loadings were allowed to change over time (configural invariance, Supplement 1). Specifically, factor loadings for the IPQ-R-dimensions increased over time from baseline, implying a gradually increasing influence of illness perceptions on psychosocial wellbeing.

In the CLPM, better psychosocial wellbeing predicted lower DAS28-CRP at each following time point, except between weeks 52 and 104 (Figure 4). Moreover, DAS28-CRP negatively predicted future psychosocial wellbeing after similar adjustments. However, contrary to other time points, this effect was positive between baseline and week 16, with higher DAS28-CRP at baseline associated with better week 16 wellbeing.

Discussion

Our results suggest that psychosocial wellbeing and illness perceptions, from as early as treatment initiation, are associated with the probability of achieving sustained remission in early RA, and that the relationship between disease activity and psychosocial factors is complex and disease-phase specific.

These results are in line with previous studies that have shown an association between mental health in early RA and the response to treatment (38). Interestingly, this is not limited to early disease, since mental health has also been shown to predict flares in patients with established RA during treatment tapering (39). Furthermore, conditions like fibromyalgia syndrome are linked with a higher prevalence of psychological vulnerability factors, including neuroticism, over resilience factors like optimism (40), and fibromyalgia-like traits such as pain catastrophizing and somatization have similarly been associated with impaired outcomes in RA (41,42). Nonetheless, the existing literature on RA has mainly focused on the influence of anxiety and depression on outcomes (43,44). To our knowledge, our approach is unique because we additionally assessed illness perceptions and coping mechanisms, and applied methods, like LPA and CFA, that studied the behavior and influence of multiple psychosocial indicators as one overarching construct, rather than as individual factors. Moreover, previous research has largely been unable to unravel the complex interplay between psychosocial and physical factors, both of which may influence each other in either direction. Our study not only reports a variety of longitudinally collected psychosocial indicators, but also applied methods that provide more information on the directionality of these relations. Specifically, our results suggest that psychosocial aspects and disease activity exert a complex, bidirectional influence on each other, with better psychosocial wellbeing predicting lower

future disease activity and vice versa. Interestingly however, this relationship appeared to function differently during the earliest disease stages, with higher disease activity at baseline being associated with better wellbeing after 4 months in our study. While somewhat counterintuitive, this suggests a stronger beneficial effect of treatment on psychosocial wellbeing in those patients who initially had the highest disease burden. Similarly, this finding might imply that psychosocial issues not directly related to disease activity are less responsive to antirheumatic treatment.

Of note, temporal relationships between wellbeing and disease activity were significant only during the first year of treatment. However, this is likely confounded by the considerably longer interval between assessments of psychosocial wellbeing during the trial's second year, possibly allowing for unrelated influences on wellbeing in the interim.

To add further insight into the complex interplay between psychosocial wellbeing and disease activity, our results also show that psychosocial wellbeing may differ among patients even when in remission, with approximately 20% of patients in DAS28-CRP- or CDAI-remission after 4 months of treatment showing markedly worse psychosocial outcomes at that time. The observation that these patients then tended to lose remission earlier than patients with a lower psychosocial burden further underlines the need for a continued attention for psychosocial wellbeing, even when clinical treatment targets are met. These findings add to those of a recent study that identified similar subgroups with either positive or negative illness perceptions among a mixed cohort of patients with early and established RA (45). However, our observation of such subgroups among patients in remission further emphasizes that psychosocial unmet needs are frequent and relevant even when the disease appears

well-controlled. Therefore, future research should aim to develop tools to help clinicians to timely identify patients with such unmet needs in clinical practice.

Our results also provide a unique insight into the evolution of illness perceptions during the early stages of RA. Before treatment, illness perceptions appeared to be highly heterogeneous among patients, and were not convincing baseline predictors of sustained remission. At week 16, however, a distinct cluster of patients could be identified who exhibited more negative illness perceptions despite being in remission. Furthermore, all included IPQ-R-dimensions at week 16 were significantly associated with sustained remission, and the relative contribution of illness perceptions to psychosocial wellbeing in the CFA also increased over time. These findings suggest that illness perceptions need time to evolve, and gain in importance once the first treatment effects have taken hold. Indeed, it has previously been shown that a person's beliefs about their illness can evolve over time, because of changes in symptoms and efforts to cope with these (46). Moreover, a recent longitudinal study from the UK identified three distinct trajectories of evolving illness perceptions during the first treatment year in patients with early RA (47). Our results add to this by illustrating that a distinct subgroup of patients with negative illness perceptions can even be identified among patients who are in remission, and that patients belonging to this subgroup have less favorable clinical outcomes.

Of additional note, illness coherence in our study appeared to be more strongly associated with long-term disease control than other dimensions of illness perception before treatment initiation. This suggests that a correct understanding of the disease early on is key for successful management of RA, while the heterogeneity in other IPQ-R-dimensions might more strongly reflect temporary uncertainties in the early phase of the disease, which to

many patients remains a destabilizing time. It is only later, after experiencing a satisfactory treatment response, that illness perceptions appear to become more uniformly shaped in most patients.

Our study has some limitations. First, we defined remission based on DAS28-CRP for our primary outcomes. A pitfall of DAS28-based remission is that it allows for some residual disease activity (48) compared to the more stringent ACR-EULAR Boolean remission or index definitions (32). However, we opted for DAS28-CRP-remission as primary outcome because it was also the primary outcome for the CareRA-trial's main analyses, and treatment during the trial was adapted when the minimal target of DAS28-LDA was not achieved. Furthermore, in our sensitivity analysis, defining remission based on CDAI produced comparable results to DAS28-based remission, which was also the case for SDAI-LDA. Regrettably, the limited number of patients achieving a sustained state of Boolean or SDAI-remission did not allow for results to be reproduced for these definitions. Therefore, our results warrant further confirmation in a larger number of patients in stringent remission. Furthermore, we should note that our choice of sustained remission as the primary outcome, rather than remission at one given time, might have reduced the discriminatory power of our analyses. For instance, patients with a short-term flare-up in PGA or CRP, which might result from issues other than RA, did not achieve sustained remission according to our definition. To illustrate this, the number of patients achieving sustained CDAI-remission in our study was markedly higher than for sustained SDAI-remission, suggesting that some patients lost SDAI-remission at least once because of solitary CRP-increases unrelated to RA disease activity.

As a second limitation, a current diagnosis or treatment of depression/anxiety was surprisingly not associated with sustained remission in our study. These results are likely

hampered by the relatively few patients with depression or anxiety in our cohort, when compared to other early RA cohorts. As a likely explanation, psychiatric co-morbidities were not screened for by a designated questionnaire but defined by anamnesis of medical history and review of medication. Consequently, it is likely that depression/anxiety were underreported in our study.

Third, missing data were imputed with multiple imputation, which assumes missingness at random. Before making this assumption, several exploratory analyses were conducted to discern systematic patterns of missingness. Moreover, efforts were made during the trial to minimize missingness, including frequent monitoring of data and specific participant education. In addition, participants who were lost to follow-up in CareRA were spread evenly across treatment arms, and reasons for discontinuation were mostly practical (18).

Finally, this study is a post-hoc analysis of a randomized controlled trial. Therefore, definite conclusions cannot be made about the causality of associations, and the number of patients in our cohort is rather limited when compared to large registry studies. However, the pragmatic nature of the CareRA-trial provided an early RA cohort that is very representative for daily practice. Furthermore, the extensive set of PROs collected at different times during early disease is a clear strength and allows for a unique translation of psychosocial burden and its clinical impact.

In conclusion, indicators of suboptimal psychosocial wellbeing during early disease were associated with a lower probability of achieving and maintaining remission in an early RA clinical trial cohort, despite intensive treat-to-target therapy. Temporal relationships between disease activity and psychosocial wellbeing appeared to be complex, bidirectional and disease-phase dependent. Crucially, 20% of patients still exhibited worse psychosocial

outcomes and more negative illness perceptions despite being in early clinical remission, and these patients tended to lose remission earlier than patients with more positive psychosocial profiles. Moreover, illness perceptions appeared to become more clinically relevant after 4 months of treatment, suggesting that the stressful period around diagnosis might not be the ideal time to evaluate psychosocial disease impact. Future research should focus on strategies to timely identify patients with unmet psychosocial needs in clinical practice and on person-centered interventions to target these needs.

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Table 1. Baseline characteristics of patients by sustained remission status.

	No sustained remission (n=255)	Sustained remission (n=124)	p-value
Demographic variables			
Age, years	52 (13)	52 (13)	0.77
BMI, kg/m^2	27 (4)	26 (4)	**0.039**
Women, n (%)	177 (69)	85 (69)	0.86
Smokers, n smoked ever (%)	146 (57)	63 (51)	0.15
RF positive, n (%)	170 (67)	82 (66)	0.92
ACPA positive, n (%)	168 (66)	81 (65)	0.91
Erosive disease, n (%)	65 (25)	32 (26)	0.95
Depression/anxiety, n (%)	8 (3)	4 (3)	0.96
Clinical variables			
DAS28-CRP	4.7 (1.2)	4.1 (1.2)	**<0.001**
TJC28, median (IQR)	9 (8)	5 (7)	**<0.001**
SJC28	7 (7)	5 (6)	**0.003**
PGA, mm (0-100)	58 (23)	49 (24)	**<0.001**
Pain, mm (0-100)	59 (24)	50 (24)	**<0.001**
Fatigue, mm (0-100)	52 (23)	40 (24)	**<0.001**
PhGA, mm (0-100)	55 (19)	47 (19)	**0.004**
ESR, mm/h, median (IQR)	25 (31)	21 (27)	0.12
CRP, mg/L, median (IQR)	26 (82)	15 (46)	0.08
HAQ (0-3), median (IQR)	1.1 (1.0)	0.8 (0.9)	**<0.001**

Results are reported as mean (SD) unless otherwise specified. *IQR = interquartile range, BMI = body mass index, RF = rheumatoid factor, ACPA = anti-citrullinated peptide antibody, DAS28 = Disease Activity Score in 28 joints, CRP = C-reactive protein, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, PGA = patient's global assessment of disease activity, PhGA = physician's global assessment of disease activity, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire*

Table 2. Psychosocial variables at baseline and week 16 predicting sustained remission.

	Baseline			Week 16		
Variable	**OR (95% CI)**	**Z-value**	**P-value**	**OR (95% CI)**	**Z-value**	**P-value**
SF-36						
SF-36MCS	1.33 (1.08 – 1.64)	2.61	**0.011**	1.84 (1.38 – 2.45)	4.15	**<0.001**
SF-36VT	1.25 (1.11 – 1.41)	3.67	**<0.001**	1.44 (1.25 – 1.65)	4.90	**<0.001**
SF-36SF	1.17 (1.07 – 1.28)	3.38	**<0.001**	1.42 (1.25 – 1.62)	5.15	**<0.001**
SF-36MH	1.23 (1.08 – 1.40)	3.02	**0.003**	1.48 (1.26 – 1.74)	4.50	**<0.001**
SF-36RE	1.06 (1.00 – 1.12)	2.04	**0.047**	1.19 (1.10 – 1.29)	4.16	**<0.001**
IPQ-R						
Illness coherence	1.06 (1.00 – 1.13)	1.92	0.052	1.11 (1.04 – 1.19)	2.73	**0.006**
Treatment control	1.07 (0.97 – 1.17)	1.30	0.188	1.18 (1.07 – 1.31)	2.65	**0.008**
Personal control	1.02 (0.96 – 1.09)	0.49	0.521	1.08 (1.00 – 1.17)	1.97	**0.048**
Emotional representations	0.98 (0.94 – 1.02)	-0.85	0.357	0.94 (0.90 – 0.98)	-2.77	**0.005**
Consequences	0.97 (0.92 – 1.02)	-1.18	0.277	0.88 (0.83 – 0.93)	-4.20	**<0.001**
UCL						
Active tackling	0.99 (0.92 – 1.06)	-0.24	0.841	1.07 (0.99 – 1.15)	1.38	0.156
Palliative reacting	0.98 (0.92 – 1.05)	-0.44	0.685	0.97 (0.91 – 1.05)	-1.09	0.303
Avoidance	0.98 (0.91 – 1.05)	-0.68	0.508	0.96 (0.89 – 1.04)	-1.35	0.175
Seeking social support	1.04 (0.97 – 1.12)	1.19	0.224	1.06 (0.98 – 1.15)	1.40	0.168
Passive reacting	0.92 (0.85 – 0.99)	-2.14	**0.037**	0.93 (0.86 – 1.01)	-1.76	0.086
Expression of emotion	1.01 (0.88 – 1.16)	0.32	0.727	1.10 (0.94 – 1.28)	0.99	0.340
Reassuring thoughts	0.98 (0.89 – 1.08)	-0.46	0.666	1.03 (0.93 – 1.13)	0.42	0.625

Results were obtained from multivariate logistic regression models with the specified variables as predictors and the odds of sustained DAS28-CRP-remission (from week 16 to week 104) as the dependent variable. All models contained age, gender, treatment arm, the presence of autoantibodies and 2C-DAS28 as covariates. *OR = odds ratio, CI = confidence interval; SF-36 = Short Form 36, MCS = mental component score, VT = vitality, SF = social functioning, MH = mental health, RE = role emotional; IPQ-R = Revised Illness Perception Questionnaire; UCL = Utrecht Coping List; 2C-DAS28 = two-component Disease Activity Score in 28 joints*

Figure 1. Flow chart of statistical analyses.

Figure 2. Psychosocial profiles among patients in DAS28-CRP-remission at week 16, based on Latent Profile Analysis (LPA).

LPA of patients in DAS28-CRP-remission at week 16, based on 9 psychosocial variables. Crossbars represent mean ± SD. Optimal model fit was obtained for 2 profiles. The low-psychosocial-burden profile consisted of 231/287 patients (80%), the high-psychosocial-burden profile of 56/287 patients (20%). *IPQ-R = Revised Illness Perception Questionnaire; SF-36 = Short Form 36*

Figure 3. Kaplan-Meier-curves for retention of DAS28-CRP-remission (A) or CDAI-remission (B) by psychosocial profile of patients in remission at week 16.

Profiles resulted from LPA of patients in remission at week 16 based on DAS28 (A) or CDAI (B). Significance was assessed by Cox-proportional hazards regression adjusting for age, gender, treatment arm, and autoantibody status. *LPA = Latent Profile Analysis*, *DAS28-CRP = Disease Activity Score in 28 joints, CDAI = Clinical Disease Activity Index*

Figure 4. Cross-lagged panel analysis of the association between psychosocial wellbeing and DAS28-CRP.

Displayed are three types of relations: within-time correlations (vertical arrows), within-construct or stability relations (horizontal arrows), and cross-lagged relations (diagonal arrows). Numbers shown are standardized regression coefficients. Paths of the observed psychosocial variables and covariates (age, gender, treatment arm and autoantibody status) were not shown for clarity.
** = p < 0.05, ** = p < 0.01, *** = p < 0.001*

Declarations

Ethics approval and consent to participate: The study protocol (S51411; EudraCT number 2008-007225-39) was approved by the University Hospitals Leuven Ethics Committee and all participants provided written informed consent before participation.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: PV, JJ and RW designed the study protocol in collaboration with the CareRA study group. Investigators of the CareRA study group, including PV and RW recruited and enrolled patients and were responsible for daily patient management. PV and JJ were responsible for coordination of the trial and collection of data. MD analyzed the data and drafted the article. DDC, PV, RW, SP and DB revised the article critically for content. All authors gave final approval of the manuscript to be published.

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