Depressive mood and low social support are not associated with arthritis development in patients with seropositive arthralgia, although they predict increased musculoskeletal symptoms

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ABSTRACT

Objective Studies on the role of psychosocial vulnerability in the development of arthritis must be performed early in the disease course to exclude the reverse explanation that arthritis leads to psychological symptoms. Therefore, the objective of this study was to investigate the longitudinal (5-year) association between depressive mood, daily stressors, avoidance coping and social support as predictors, and the development of arthritis and other clinical parameters as outcomes, in persons with seropositive arthralgia at risk of developing rheumatoid arthritis.

Methods Five-year follow-up data of 231 patients from the Reade seropositive arthralgia cohort were used. Clinical and psychological data were collected using physical examinations and questionnaires. Mixed models and Cox regression analyses were used to assess the 5-year associations between depressive mood, daily stressors, avoidance coping or social support, and the development of arthritis or clinical parameters.

Results Higher scores for depressive mood and lower scores for social support were not associated with the development of arthritis nor with ESR. However, they were longitudinally associated with an increase in pain (p<0.001), morning stiffness (p<0.01) and tender joint count (p<0.001). No consistent associations were found between daily stressors, avoidance coping and the development of arthritis or other clinical parameters.

Conclusion Although an effect on the development of arthritis could not be demonstrated, a strong longitudinal association was found between high depressive mood, low social support and clinical parameters. In persons with seropositive arthralgia, depressive symptoms and low social support may increase musculoskeletal symptoms.

INTRODUCTION

Depression is highly prevalent in persons with rheumatoid arthritis (RA). A meta-analysis of studies reporting prevalence estimates for depression in RA revealed rates between 15% and 40%, depending on the manner in which depression was measured.1 Depression is also common in diseases that are associated with...
RA through shared pathogenic factors, such as cardiovascular diseases and diabetes mellitus, and may even increase the risk of developing these diseases. It seems that persons with depression also have an increased risk of developing RA; however, this risk is less well established. Likewise, post-traumatic stress disorder has been associated with an elevated risk of the development of RA and increased RA disease activity, and perceived stress has been associated with self-reported arthritis development 3 years later in women. In addition, studies point to an unfavourable course of disease activity in patients with RA with symptoms of depression. The same holds true for avoidance coping and lack of social support, which also have been associated with increased disease activity in persons with RA. Finally, besides indications for an unfavourable disease course, it has been shown that persons with RA and depression generally have reduced treatment response and poorer health status, with as a result an increased risk of mortality and work disability already at an early stage of RA.

Several mechanisms have been described that may partially explain the increased cardiovascular risk in persons with depression, including unhealthy behaviours, pathophysiological dysregulations (immune system, hypothalamic–pituitary–adrenal axis (HPA axis) and metabolic), shared genetic vulnerability and residual confounding. These mechanisms are not disease-specific, and may also explain the link between depression and RA. Although depression has been linked to disease activity in persons with RA, results of longitudinal studies on this relationship are inconsistent. Most studies reported positive associations between higher scores of depression (or scores above a certain cut-off) on one hand, and smaller reductions in disease activity scores, a lower proportion of clinical remission and a lower reduction of pain on treatment, on the other hand. However, two studies could not confirm these positive associations. Explanations may be the difference in follow-up times, that is, 1–3.5 years for the positive studies and 5–10 years for the negative studies, different active treatment schedules which might have the biggest effect on the studies with shorter follow-up times, and the bidirectional association between depression and RA. It is likely that the first symptoms and the diagnosis of RA lead to a depressive mood, whereas active treatment aims to reduce disease activity which in turn will lead to an improved mood. To exclude the reverse explanation that RA symptoms and treatment lead to changes in mood, studies on the influence of depressive mood on the onset of RA must be performed as early in the disease course as possible. It is important to know whether depression increases the risk of developing RA. If this is the case, treatment of depression could contribute to the prevention of arthritis.

Two studies have investigated the bilateral association between depressive mood and RA development in cohorts of persons without active RA or treatment for RA at the moment of inclusion. The first found a bidirectional relation between RA and depression in a Taiwanese health insurance database, and the second found that self-reported arthritis predicts the development of mood and anxiety disorders, and no reverse association was found. These studies did not analyse the association between depressive mood and measures of disease activity or symptoms, and may have misclassified patients by using the International Classification of Diseases, Ninth Revision, Clinical Modification codes or self-report to identify patients with RA or depression. Therefore, we studied the longitudinal association between depressive mood, daily stressors, avoidance coping and social support as predictors, and the development of arthritis and clinical parameters (ie, pain, morning stiffness, tender joint count and erythrocyte sedimentation rate (ESR)) as outcomes, in patients with seropositive arthropathy at risk for developing RA. This is the first study that used physician-based diagnoses to explore these associations in a cohort with an increased risk for RA, but without overt inflammation (ie, normal ESR values and no swollen joints). Depressive mood, daily stressors and clinical parameters were considered the primary predictors and outcomes, respectively.

**PATIENTS AND METHODS**

**Study design and population**

A 5-year follow-up study of a sample of 235 patients from the Reade seropositive arthralgia cohort (included between August 2004 and January 2011) was undertaken. This cohort was formed to identify clinical and serological predictors for the development of arthritis (90% of whom fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA), and recruited persons with arthralgia and positive anticitrullinated protein antibodies and/or IgM-rheumatoid factor status. Demographic, clinical and laboratory measurements were performed every year until a complete follow-up of 5 years or arthritis development. Details on the study protocol have been published elsewhere. All cohort participants were eligible for the present study and were sent questionnaires measuring depressive mood, daily stressors, avoidance coping and social support between March 2008 and January 2016. Questionnaires were only sent to patients without a diagnosis of arthritis, as it was explicitly the intention to investigate the relation of psychological parameters with the development of arthritis, and not with the period thereafter. Please note that baseline descriptives (table 1) were taken at baseline of the present study. This means some patients turned out seronegative at baseline, while they were seropositive when entering the parent study. Patients included between April 2006 and January 2011 were sent questionnaires simultaneously with the clinical measurements at baseline, 3-year, 4-year and 5-year follow-up (n=199). Patients included between April 2005 and April 2006 (n=22) were sent questionnaires after 3, 4 and 5 years, and patients included between August 2005 and April 2006 (n=22) were sent questionnaires after 3 years later in women.
Inflammatory arthritis

2004 and March 2005 (n=14) were sent questionnaires after 4 and 5 years of follow-up. All patients gave their written informed consent before entering the cohort study and were additionally invited to complete the questionnaires.

### Table 1 Characteristics of the 231 patients with arthralgia at the time of the first questionnaire

| Characteristics                      | Total (n=231) | Patients who were diagnosed with arthritis during the study (n=79) | Patients who were not diagnosed with arthritis (n=152) |
|--------------------------------------|--------------|-----------------------------------------------------------------|-------------------------------------------------------|
| Age (years), mean (SD)              | 49.6 (11.4)  | 47.6 (11.0)                                                     | 50.6 (11.6)                                           |
| Gender (female), n (%)              | 179 (77.5)   | 62 (78.5)                                                       | 117 (77.0)                                           |
| Duration of symptoms (months), median (IQR) | 17.1 (11.9–36.4) | 17.1 (9.3–36.1)                                             | 17.1 (12.0–36.5)                                     |
| IgM-RF and ACPA status              |              |                                                                |                                                      |
| IgM-RF-positive, ACPA-negative, n (%) | 73 (31.6)    | 8 (10.1)                                                        | 65 (42.8)                                             |
| ACPA-positive, IgM-RF-negative, n (%) | 97 (42.0)    | 40 (50.6)                                                      | 57 (37.5)                                             |
| IgM-RF and ACPA-positive, n (%)     | 50 (21.6)    | 31 (39.2)                                                      | 19 (12.5)                                             |
| IgM-RF and ACPA-negative, n (%)     | 11 (4.8)     | 0 (0)                                                          | 11 (7.2)                                              |
| ESR (mm/hour), median (IQR)         | 12.5 (6.0–20.0) | 12.5 (4.0–21.3)                                             | 12.5 (7.0–20.0)                                      |
| VAS pain (range: 0–100), median (IQR) | 26 (0–50)   | 33 (15–60)                                                     | 23 (0–48)                                             |
| VAS morning stiffness (range: 0–100), median (IQR) | 14 (0–42) | 26 (0–59)                                                      | 0 (0–33)                                              |
| Tender joint count 53 (range: 0–53), median (IQR) | 0 (0–3) | 1 (0–5)                                                        | 0 (0–2)                                               |
| HADS depression score (range: 0–21), median (IQR) | 4 (1–7) | 4 (2–8)                                                        | 4 (1–7)                                               |
| HADS score ≥8 (suggestive of the presence of depressed mood), n (%) | 54 (23.4) | 20 (25.3)                                                     | 34 (22.4)                                             |
| HADS score ≥11 (probable presence of depression), n (%) | 24 (10.4) | 12 (15.2)                                                      | 12 (7.9)                                              |
| Everyday Problem Checklist score (range: 0–49), median (IQR) | 10 (6–16) | 10 (6–17)                                                     | 10 (6–15)                                             |
| UCL avoidance score (range: 8–32), mean (SD) | 15.7 (3.3) | 15.4 (3.1)                                                    | 15.8 (3.4)                                            |
| IRGL perceived support score (range: 5–20), median (IQR) | 15 (12–18) | 15 (14–18)                                                    | 15 (12–19)                                            |
| Follow-up time (months), median (IQR) | 33 (13–59)  | 12 (5–25)                                                      | 48 (23–60)                                            |

ACPA, anticitrullinated protein antibodies; ESR, erythrocyte sedimentation rate; HADS, Hospital Anxiety and Depression Scale; IRGL, Impact of Rheumatic Diseases on General Health and Lifestyle; RF, rheumatoid factor; UCL, Utrecht Coping List; VAS, Visual Analogue Scale.

### Questionnaire items

The primary independent variables were depressive mood, measured with the depression subscale of the Hospital Anxiety and Depression Scale (HADS), and daily stressors, measured with the 49-item version of the Everyday Problem Checklist (EPCL). The secondary independent variables were avoidance coping, measured with the avoidance subscale of the Utrecht Coping List (UCL), and social support, measured with the perceived support scale of the Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL) questionnaire.

### The Hospital Anxiety and Depression Scale

The HADS depression subscale comprises seven items that are answered on a 4-point scale. The sum score ranges from 0 to 21, with a higher score indicating a more depressive mood. This sum score was used in analyses. In addition, we calculated cut-off scores to describe the degree of depressive mood in a more discrete way. These cut-off scores are based on the findings of Zigmond and Snaith, who reported that a score of 8–10 is suggestive
of the presence of a depressive disorder and a score ≥11 indicates probable presence (‘caseness’) of a depressive disorder. Both the sum score and the cut-off scores are presented in table 1. The HADS is widely used in clinical research and has been shown to be reliable for use as a screening tool in different groups of Dutch adults aged 18–65 years (Cronbach’s alpha: 0.77–0.86).

The Everyday Problem Checklist

The EPCL comprises 49 items that describe irritating, annoying or disappointing events and situations, for which the patient has to indicate whether he or she had dealt with it in the past 4 weeks. The sum score ranges from 0 to 49, with a higher score indicating more daily stressors. The reliability of the EPCL sum score has been shown to be satisfactory in Dutch adults.

The Utrecht Coping List

The avoidance subscale of the UCL comprises eight items that are answered on a 4-point scale. The sum score ranges from 8 to 32, with a higher score indicating a more frequent use of avoidance coping. The UCL avoidance subscale has been shown to be sufficiently reliable in Dutch adults (Cronbach’s alpha: 0.74–0.76).

The perceived support scale of the Impact of Rheumatic Diseases on General Health and Lifestyle questionnaire

The perceived support subscale of the IRGL comprises five items that are answered on a 4-point scale. The sum score ranges from 5 to 20, with a higher score indicating a higher perception of social support. The IRGL perceived support scale has been shown to be highly reliable in Dutch adults (Cronbach’s alpha: 0.94).

Statistical analyses

First, we explored changes in depressive mood, daily stressors, avoidance coping and social support between baseline and 5-year follow-up using descriptive statistics.

Second, we performed Cox regression analyses with time-dependent covariates to analyse the association between the independent variables depressive mood, daily stressors, avoidance coping and social support, and the development of arthritis. Hereby, the independent variables were time-updated to use all available questionnaire sum scores at the different time points. All independent variables were included as continuous variables in the Cox analyses. An additional analysis was done with depression as a dichotomous variable (HADS depression score ≥11) to facilitate interpretation (table 2, model 1b).

Third, mixed models with a random intercept were used to evaluate the longitudinal associations between the independent variables depressive mood, daily stressors, avoidance coping and social support (measured on a continuous scale), and the outcome variables VAS pain, VAS morning stiffness, TJC53 and ESR. In our design we took multiple measures per individual. That is, each individual completed multiple questionnaires at multiple times and was clinically assessed at the same moments. Multiple responses from the same individual cannot be regarded as independent from each other; however, linear mixed effects models correct for this independence. This implies that measured variables at all time points were included in the models. Separate analyses were performed for both the four independent variables and the four dependent variables. The random intercept accounts for the correlated nature of multiple measurements from the same individual. To distinguish between ‘between-subject’ and ‘within-subject’ effects, in addition, hybrid mixed models were performed.

Depending on the distribution of the outcome variable, we used different mixed models. Tobit mixed model analyses were performed for the two VAS scores, taking into account left censoring. Negative binomial mixed models were used for TJC53 and linear mixed models for ESR. Before the analyses, ESR was log-transformed because of skewness to the right. We identified age, gender and symptom duration as potential confounders. In step 2 of all analyses we adjusted for these variables.

Mixed models were computed using Stata V.14, and Cox regression analyses were performed with SPSS V.21.

### Table 2

| Model  | Independent variables | Development of arthritis |
|--------|-----------------------|--------------------------|
|        |                       | HR | 95% CI   | P values |
| 1a (n=228) | Depressive mood (HADS depression score) | 1.04 | 0.98 to 1.09 | 0.208 |
| 1b (n=228) | Depressive mood (HADS depression score ≥11) | 1.82 | 0.96 to 3.44 | 0.068 |
| 2 (n=230) | Daily stressors (EPCL frequency score) | 1.01 | 0.99 to 1.04 | 0.352 |
| 3 (n=227) | Avoidance coping (UCL avoidance score) | 0.98 | 0.91 to 1.05 | 0.577 |
| 4 (n=231) | Social support (IRGL perceived support score) | 0.98 | 0.92 to 1.04 | 0.438 |

The independent variables depressive mood, daily stressors, avoidance coping and social support were time-updated. In all models, adjustment for age, gender and symptom duration did not change the results (data not shown).

EPCL, Everyday Problem Checklist; HADS, Hospital Anxiety and Depression Scale; IRGL, Impact of Rheumatic Diseases on General Health and Lifestyle; UCL, Utrecht Coping List.
RESULTS

Study population
Of the 235 persons invited to participate in the study, 4 persons completed none of the questionnaires and were therefore excluded. Of the remaining 231 patients, 79 (34.2%) developed arthritis during the study, after a median of 12 (25th–75th percentiles 5–25) months. Postarthritis no further questionnaires were sent to these patients. In all patients who should have completed the questionnaire at the different time points (taking into account ‘dropouts’ due to the incident diagnosis of arthritis), 185 (80.1%), 118 (72.4%), 116 (71.2%) and 99 (62.7%) patients completed the baseline, 3-year, 4-year and 5-year follow-up questionnaires, respectively. The characteristics of the study population at the time of the first questionnaire are presented in table 1.

Changes in depressive mood, daily stressors, avoidance coping and social support

Very small changes in HADS depression score (median (IQR) at T0=4 (1–7), T3=3 (1–7), T4=3 (1–7), T5=3 (1–6)), EPCL daily stressors score (median (IQR) at T0=10 (6–16), T3=10 (6–15), T4=9 (5–14), T5=10 (5–15)), UCL avoidance score (mean±SD at T0=15.7±3.3, T3=15.5±3.0, T4=15.5±3.1, T5=15.5±3.1) and IRGL perceived support score (median (IQR) at T0=15 (12–18), T3=15 (12–18), T4=15 (13–19), T5=15 (12–18)) were observed between baseline and 5-year follow-up.

Development of arthritis

The Cox regression analyses revealed no statistically significant associations between depressive mood, daily stressors, avoidance coping or social support, and the development of arthritis (HRs of between 0.98 and 1.04; table 2). The results did not change after adjustment for potential confounders.

Clinical parameters

Depressive mood and daily stressors

Regular and hybrid tobit mixed models showed that the HADS depression score was statistically significantly associated with VAS pain (regression coefficient (B) 2.34, 95% CI 1.59 to 3.08, p<0.001) and VAS morning stiffness (B 4.09, 95% CI 1.18 to 7.00, p=0.006) (table 3). The regression coefficients of 2.34 and 4.09 have a combined between-subject (ie, cross-sectional) and within-subject (ie, longitudinal) interpretation, and can be interpreted as follows: a one-unit difference in the HADS depression score between two patients or a one-unit increase in the HADS depression score within one patient, then the TJC53 will be 1.06 times higher. Bs and RRs can be split into a between-subject (ie, cross-sectional) and within-subject (ie, longitudinal) effect, which are presented in table 3. For VAS pain, the between-subject effect and the within-subject effect were both statistically significant; however, the between-subject effect was stronger, indicating greater differences in pain between two patients with different HADS depression scores (cross-sectional) than changes in pain within patients with changing HADS scores (longitudinal). For VAS stiffness and TJC53, only the between-subject effect was significantly associated with HADS depression scores. HADS depression scores and ESR were not associated (Exp(B) 1.01, 95% CI 0.99 to 1.03, p=0.23). The regression coefficient of log-transformed ESR was back-transformed to Exp(B), and can be interpreted like the RR as presented above. Daily stressors were only significantly associated with VAS pain (B 0.44, 95% CI 0.04 to 0.84, p=0.03), attributed mainly by the cross-sectional differences in scores between patients. None of the results changed after correction for potential confounders (online supplementary table 1).

Avoidance coping and social support

Higher social support was significantly associated with lower VAS pain (B −1.97, 95% CI −2.77 to −1.17, p<0.001), VAS morning stiffness (B −4.33, CI −7.40 to −1.28, p=0.005) and TJC53 (RR 0.95, 95% CI 0.91 to 0.96, p<0.001) scores (table 3). No statistically significant longitudinal associations were found between avoidance coping and disease activity measures.

DISCUSSION

This is the first prospective study that investigated the association between depressive mood, daily stressors, avoidance coping, social support and progression towards arthritis or clinical parameters in patients at risk of developing RA. An effect on the development of arthritis and its timing could not be demonstrated. However, we did find a strong association between high depressive mood, low social support and several clinically important parameters, such as VAS pain, VAS morning stiffness and TJC53. No consistent associations were found between daily stressors, avoidance coping and any of the clinical parameters.

One can speculate about the mechanism by which high depressive mood is associated with higher clinical parameter scores in these patients: is it purely psychological or also biological? As a person’s psychological state plays a key role in the experience and expression of (joint) symptoms and vice versa, a psychological mechanism seems likely. Depressive symptoms and stress are believed to influence clinical parameters via negative perceptions of symptoms and non-adherence to medical recommendations. However, it is also possible that depression leads partly to a higher presence of clinical parameters
| Independent variables              | VAS pain       | VAS morning stiffness | Tender Joint Count 53 | Erythrocyte Sedimentation Rate |
|-----------------------------------|----------------|-----------------------|-----------------------|--------------------------------|
|                                   | B 95% CI Obs   | B 95% CI Obs          | RR 95% CI Obs         | Exp(B) 95% CI Obs             |
| 1 Depressed mood (HADS depression score) | 2.34 1.59 to 3.08 886 | 4.09 1.08 to 7.00 892 | 1.06 1.03 to 1.09 894 | 1.01 0.99 to 1.03 821 |
| Between-subject effect            | 2.63 1.76 to 3.50 | 4.62 1.34 to 7.89     | 1.08 1.04 to 1.12     | 1.03 1.00 to 1.06            |
| Within-subject effect             | 1.55 0.11 to 2.98 | 2.14 −4.14 to 8.41   | 1.02 0.97 to 1.08     | 1.00 0.98 to 1.02            |
| 2 Daily stressors (EPCL frequency score) | 0.44 0.04 to 0.84 892 | 0.31 −1.19 to 1.80 898 | 1.01 0.99 to 1.02 900 | 1.00 0.99 to 1.01 827 |
| Between-subject effect            | 0.59 0.11 to 1.07 | −0.15 −1.89 to 1.58   | 1.01 0.99 to 1.03     | 1.01 0.99 to 1.02            |
| Within-subject effect             | 0.12 −0.59 to 0.83 | 1.67 −1.32 to 4.66   | 0.99 0.97 to 1.02     | 1.00 0.98 to 1.01            |
| 3 Avoidance coping (UCL avoidance score) | 0.47 −0.49 to 1.42 883 | −0.66 −4.22 to 2.89 889 | 1.03 1.00 to 1.07 891 | 0.99 0.97 to 1.01 818 |
| Between-subject effect            | 1.03 −0.15 to 2.21 | −0.22 −4.38 to 3.94   | 1.01 0.97 to 1.07     | 1.02 0.98 to 1.06            |
| Within-subject effect             | −0.58 −2.19 to 1.02 | −1.87 −8.74 to 4.99   | 1.05 0.99 to 1.12     | 0.98 0.96 to 1.01            |
| 4 Social support (IRGL perceived support) | −1.97 −2.77 to −1.17 892 | −4.34 −7.40 to −1.28 898 | 0.93 0.91 to 0.96 900 | 1.00 0.98 to 1.02 826 |
| Between-subject effect            | −2.24 −3.23 to −1.25 | −3.65 −7.26 to −0.05  | 0.93 0.89 to 0.97     | 1.00 0.96 to 1.03            |
|Within-subject effect              | −1.47 −2.82 to −0.12 | −6.11 −11.93 to −0.30 | 0.94 0.90 to 0.99     | 1.00 0.98 to 1.02            |

B, regression coefficient; analysed with linear mixed models analyses taking into account left censoring. RR, rate ratio; analysed with negative binomial mixed models taking into account left censoring in a variable in which a score of 0 really means zero. Exp(B), exponent (regression coefficient); analysed with linear mixed models in which ESR was log-transformed (ln(ESR)) because of skewness to the right. Hybrid mixed models were used to split the Bs and RRs into a between-subject (ie, cross-sectional) and within-subject (ie, longitudinal) effect. The between-subject effect shows the difference in the outcome variable between two patients having a one-unit difference in the independent variable. The within-subject effect shows the increase in the outcome variable within one patient when the independent variable increases with one unit. In bold are statistically significant associations with a p value <0.05.

EPCL, Everyday Problem Checklist; ESR, erythrocyte sedimentation rate; HADS, Hospital Anxiety and Depression Scale; IRGL, Impact of Rheumatic Diseases on General Health and Lifestyle; Obs, number of observations of the outcome used in analysis; UCL, Utrecht Coping List; VAS, Visual Analogue Scale.
through biological mechanisms, which may or may not be induced by behaviour. Possible biological mechanisms are dysregulation of the immune system,5 16 41 HPA axis or metabolism,3 16 41 42 which may be induced by a shared genetic vulnerability leading to both depression and RA.5 A combined biological and behavioural mechanism is unhealthy lifestyle behaviours such as smoking, physical inactivity and unhealthy diet, which are risk factors for both diseases, but may also be caused by depression.43–46 Our results provide most support for a psychological mechanism, because depressive mood was mainly associated with subjectively reported clinical parameters, although we cannot rule out that the mechanism that connects depressive mood with clinical parameters is also partly biological. In our study population of patients with arthralgia without active clinical disease, we had a limited set of biological disease activity measures available.

The association of low social support with an increase in disease activity is in line with the results of a 5-year follow-up study in 78 persons with early RA.14 Social support may influence clinical parameters via negative disease-related cognitions, low self-efficacy, unfavourable coping and unhealthy behaviours.14

Besides discussing the mechanism by which depressive mood and low social support are associated with clinical parameters, one can also debate on the clinical implication of this finding. A recent study showed that the presence of depression reduced the success percentage of biological treatment in patients with RA,17 probably because pain and perceived health are taken into account in disease activity scores such as the Disease Activity Score 28, and the sense of well-being is disrupted in patients with a depressive mood. This might indicate that early detection and treatment of depressive mood may benefit future treatment in patients with arthralgia for whom interventions to prevent the development of RA are not available yet.48 The potentially important influence of social support on the course of clinical parameters is something that physicians also should be aware of. However, it may even be true that higher pain and fatigue scores are more a consequence of depression than of arthritis.

In analyses testing causal explanations, one should not adjust for variables in the causal pathway. Therefore, in the analysis between one of the four questionnaire variables (ie, depressive mood, daily stressors, avoidance coping and social support) and the outcome, we did not adjust for the other three questionnaire variables. However, to be on the safe side, we examined what happens when all questionnaire variables are included in the analyses (online supplementary table 2). The results of these analyses show that even if we adjust for variables that are potentially on the causal path, the results are almost the same.

Our study may be criticised for the fact that, although our study population consists of a seropositive arthralgia cohort without active RA or treatment, it is becoming increasingly clear that patients already experience a high burden of symptoms that adversely affect daily functioning, and in turn may affect their mood.49 50 As a result, we cannot completely rule out that early symptoms have had influence on subsequent depressive mood. Second, some patients entered the present study later than entering the prospective cohort of autoantibody-positive arthralgia. This might have introduced selection bias, as patients developing arthritis had already been censored. However, in daily practice when a particular patient with arthralgia presents to the rheumatologist, we can also only tell in retrospect the stage of preclinical RA he or she was at. Third, we did not adjust for educational level in the analyses. Although a low level of education or socioeconomic status does not appear to be a strong risk factor for the development of arthritis, it is associated with depression, daily stressors, coping behaviour and social support. Therefore, it is possible that educational level has slightly biased the association found between the psychological variables and clinical parameters.

In conclusion, our findings highlight that an effect of psychological parameters on arthritis development could not be demonstrated in patients with seropositive arthralgia. However, a strong longitudinal association was found between high depressive mood, low social support and clinical parameters. For clinicians it is important to be aware that, already in patients at risk of developing arthritis, depressive symptoms and low social support may increase musculoskeletal symptoms.

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Contributors JFMH and MHvB carried out the analysis, interpreted the data and drafted the manuscript; furthermore they are accountable for all aspects of the work. LAvD participated in designing the study, collected clinical data, helped interpret the results and helped in drafting the manuscript. RL and JWRT helped with statistical analyses, along with critically reviewing the manuscript. JD and DvS helped in the design and coordination of the study, supervised the drafting of the manuscript, and carefully reviewed the manuscript. All authors read and approved the final manuscript.

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