ORIGINAL ARTICLE

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

Jasmijn F M Holla,[1] Marian H van Beers-Tas,[2] Lotte A van de Stadt,[3] Robert Landewé,[4] Jos W R Twisk,[5] Joost Dekker,[1,6,7,8] Dirkjan van Schaardenburg[2,4]

Check for updates

For numbered affiliations see end of article.

Correspondence to
Dr Marian H van Beers-Tas; m.v.beers@reade.nl

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 (tender joint count, Visual Analogue Scale (VAS) pain, VAS morning stiffness and erythrocyte sedimentation rate (ESR)).

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.

Key messages

What is already known about this subject?
► Depression, daily stressors, avoidance coping and lack of social support have been linked to disease activity in persons with rheumatoid arthritis (RA); however, results of longitudinal studies on these relationships are inconsistent or scarce.

What does this study add?
► This is the first study that explored the predictive roles of depressive mood, daily stressors, avoidance coping and social support in the development of physician-diagnosed clinical arthritis in persons at risk of developing RA without overt inflammation.
► In persons with seropositive arthralgia, an effect of depressive mood, daily stressors, avoidance coping and social support on the development of clinical arthritis could not be demonstrated.
► However, a strong longitudinal association was found between high depressive mood and low social support, and pain, morning stiffness and tender joint count.

How might this impact on clinical practice?
► The results indicate that 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 cardio-vascular diseases and diabetes mellitus,[2 3] and may even increase the risk of developing these diseases.[4 5] It seems that persons with depression also have an increased risk of developing RA; however, this risk is less well established.[6] Likewise, post-traumatic stress disorder has been associated with an elevated risk of the development of RA and increased RA disease activity,[7–10] and perceived stress has been associated with self-reported arthritis development 3 years later in women.[11] In addition, studies point to an unfavourable course of disease activity in patients with RA with symptoms of depression.[12 13] 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.[14 15] 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.[16–18]

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.[5 19] 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.[12 13 20–25] 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,[12 13 20 22 25] a lower proportion of clinical remission[13 20] and a lower reduction of pain on treatment,[12 13 22 23 25] on the other hand. However, two studies could not confirm these positive associations.[21 24] 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.[6] 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,[6] and the second found that self-reported arthritis predicts the development of mood and anxiety disorders, and no reverse association was found.[26] 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.[6 26] 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 arthralgia 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.[27 28] 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),[28 29] 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.[28] 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

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

Characteristics	Total (n=231) Value	Patients who were diagnosed with arthritis during the study (n=79) Value	Patients who were not diagnosed with arthritis (n=152) Value
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.

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.

MEASUREMENTS
Clinical endpoints
The first endpoint was the development of arthritis, as clinically diagnosed by a trained medical doctor based on a physical examination of 44 joints. The presence of arthritis in at least one joint was always confirmed by a senior rheumatologist (DvS). At the start of our study, we did not know how many patients would progress to arthritis, and expected that changes in clinical parameters would precede the development of arthritis. Therefore, we selected a Visual Analogue Scale (VAS) for pain (range: 0–100), a VAS for morning stiffness (0–100), tender joint count 53 (TJC53) and ESR (reference <15 mm/hour for men, <20 mm/hour for women) as additional outcomes.

Questionnaire items
The primary independent variables were depressive mood, measured with the depression subscale of the Hospital Anxiety and Depression Scale (HADS),[30] and daily stressors, measured with the 49-item version of the Everyday Problem Checklist (EPCL).[31] The secondary independent variables were avoidance coping, measured with the avoidance subscale of the Utrecht Coping List (UCL),[32] and social support, measured with the perceived support scale of the Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL) questionnaire.[33]

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.[30] 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.[30 34] 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).[35]

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.[31] The sum score ranges from 0 to 49, with a higher score indicating more daily stressors. The reliability of the ECPL sum score has been shown to be satisfactory in Dutch adults.[31]

The Utrecht Coping List
The avoidance subscale of the UCL comprises eight items that are answered on a 4-point scale.[32] 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).[36]

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.[33] 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).[37]

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.[38] 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.[39]

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.[40] 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 Cox regression of the development of arthritis on depressive mood, daily stressors, avoidance coping and social support

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 (13–18), 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 is associated with a difference or increase of 2.34 and 4.09 units in the VAS pain score and VAS morning stiffness score, respectively. Regular and hybrid negative binomial mixed models showed that the HADS depression score was statistically significantly associated with TJC53 (rate ratio (RR) 1.06, 95% CI 1.03 to 1.09, p<0.001) (table 3). This can be interpreted as follows: if the HADS depression score is one-unit higher in one patient compared

with another patient, or increases with one unit 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 0.93, 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.[5][9] However, it is also possible that depression leads partly to a higher presence of clinical parameters

Table 3 Longitudinal regression of clinical parameters on depressed mood, daily stressors, avoidance coping and social support

Independent variables	VAS pain B	95% CI	Obs	VAS morning stiffness B	95% CI	Obs	Tender Joint Count 53 RR	95% CI	Obs	Erythrocyte Sedimentation Rate Exp(B)	95% CI	Obs
1 Depressed mood (HADS depression score)	**2.34**	**1.59 to 3.08**	886	**4.09**	**1.18 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 in a variable in which a score of 0 really means zero. Exp(B), exponent (regression coefficient); analysed with negative binomial mixed models taking into account left censoring. RR, rate ratio; 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,[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,[47] 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 concerns 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.

Author affiliations
[1]Amsterdam Rehabilitation Research Center, Reade, Amsterdam, The Netherlands
[2]Amsterdam Rheumatology and immunology Center, Reade, Amsterdam, The Netherlands
[3]Amsterdam Rheumatology and immunology Center, VU University Medical Center, Amsterdam, The Netherlands
[4]Amsterdam Rheumatology and immunology Center, Academic Medical Center, Amsterdam, The Netherlands
[5]Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands
[6]Department of Rehabilitation Medicine, VU University Medical Center, Amsterdam, The Netherlands
[7]Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands
[8]Amsterdam Public Health research institute, VU University Medical Center, Amsterdam, The Netherlands

REFERENCES

1. Matcham F, Rayner L, Steer S, *et al*. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology* 2013;52:2136–48.
2. Ozen G, Pedro S, Holmqvist ME, *et al*. Risk of diabetes mellitus associated with disease-modifying antirheumatic drugs and statins in rheumatoid arthritis. *Ann Rheum Dis* 2017;76:848–54.
3. Dougados M. Comorbidities in rheumatoid arthritis. *Curr Opin Rheumatol* 2016;28:282–8.
4. Yu M, Zhang X, Lu F, *et al*. Depression and risk for diabetes: a meta-analysis. *Can J Diabetes* 2015;39:266–72.
5. Penninx BW. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev* 2017;74:277–86.
6. Lu MC, Guo HR, Lin MC, *et al*. Bidirectional associations between rheumatoid arthritis and depression: a nationwide longitudinal study. *Sci Rep* 2016;6:20647.
7. Boscarino JA, Forsberg CW, Goldberg J. A twin study of the association between PTSD symptoms and rheumatoid arthritis. *Psychosom Med* 2010;72:481–6.
8. Lee YC, Agnew-Blais J, Malspeis S, *et al*. Post-traumatic stress disorder and risk for incident rheumatoid arthritis. *Arthritis Care Res* 2016;68:292–8.
9. Mikuls TR, Padala PR, Sayles HR, *et al*. Prospective study of posttraumatic stress disorder and disease activity outcomes in US veterans with rheumatoid arthritis. *Arthritis Care Res* 2013;65:227–34.
10. O'Donovan A, Cohen BE, Seal KH, *et al*. Elevated risk for autoimmune disorders in iraq and afghanistan veterans with posttraumatic stress disorder. *Biol Psychiatry* 2015;77:365–74.
11. Harris ML, Loxton D, Sibbritt DW, *et al*. The influence of perceived stress on the onset of arthritis in women: findings from the Australian Longitudinal Study on women's health. *Ann Behav Med* 2013;46:9–18.
12. Hider SL, Tanveer W, Brownfield A, *et al*. Depression in RA patients treated with anti-TNF is common and under-recognized in the rheumatology clinic. *Rheumatology* 2009;48:1152–4.
13. Kekow J, Moots R, Khandker R, *et al*. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. *Rheumatology* 2011;50:401–9.
14. Evers AW, Kraaimaat FW, Geenen R, *et al*. Stress-vulnerability factors as long-term predictors of disease activity in early rheumatoid arthritis. *J Psychosom Res* 2003;55:293–302.
15. Geenen R, Van Middendorp H, Bijlsma JW. The impact of stressors on health status and hypothalamic-pituitary-adrenal axis and autonomic nervous system responsiveness in rheumatoid arthritis. *Ann N Y Acad Sci* 2006;1069:77–97.
16. Rathbun AM, Reed GW, Harrold LR. The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: a systematic review. *Rheumatology* 2013;52:1785–94.
17. Matcham F, Norton S, Scott DL, *et al*. 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* 2016;55:268–78.
18. Callhoff J, Albrecht K, Schett G, *et al*. Depression is a stronger predictor of the risk to consider work disability in early arthritis than disease activity or response to therapy. *RMD Open* 2015;1:e000020.
19. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol Bull* 2014;140:774–815.
20. Leblanc-Trudeau C, Dobkin PL, Carrier N, *et al*. Depressive symptoms predict future simple disease activity index scores and simple disease activity index remission in a prospective cohort of patients with early inflammatory polyarthritis. *Rheumatology* 2015;54:2205–14.
21. Overman CL, Bossema ER, van Middendorp H, *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.
22. Euesden J, Matcham F, Hotopf M, *et al*. The relationship between mental health, disease severity, and genetic risk for depression in early rheumatoid arthritis. *Psychosom Med* 2017;79:638–45.
23. Zautra AJ, Smith BW. Depression and reactivity to stress in older women with rheumatoid arthritis and osteoarthritis. *Psychosom Med* 2001;63:687–96.
24. Odegård S, Finset A, Mowinckel P, *et al*. Pain and psychological health status over a 10-year period in patients with recent onset rheumatoid arthritis. *Ann Rheum Dis* 2007;66:1195–201.
25. Rathbun AM, Harrold LR, Reed GW. Temporal effect of depressive symptoms on the longitudinal evolution of rheumatoid arthritis disease activity. *Arthritis Care Res* 2015;67:765–75.
26. van 't Land H, Verdurmen J, Ten Have M, *et al*. The association between arthritis and psychiatric disorders; results from a longitudinal population-based study. *J Psychosom Res* 2010;68:187–93.
27. van de Stadt LA, Witte BI, Bos WH, *et al*. A prediction rule for the development of arthritis in seropositive arthralgia patients. *Ann Rheum Dis* 2013;72:1920–6.
28. Bos WH, Wolbink GJ, Boers M, *et al*. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. *Ann Rheum Dis* 2010;69:490–4.
29. Aletaha D, Neogi T, Silman AJ, *et al*. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;2010:2569–81.
30. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
31. Vingerhoets A, Jeninga A, Menges L. Het meten van chronische en alledaagse stressoren. II. Eerste onderzoekservaringen met de Alledaagse Problemen Lijst (APL) [The measurement of daily hassles and chronic stressors: the development of the Everyday Problem Checklist (EPCL, Dutch: APL)]. *Gedrag en Gezondheid* 1989;17:10–17.
32. Schreurs P, Tellegen B, van den Willige G. Gezondheid, stress en coping: de ontwikkeling van de Utrechtse Coping Lijst [Health, stress and coping: The development of the Utrecht Coping List]. *Gedrag: tijdschrift voor psychologie* 1984;12:101–17.
33. Huiskes C, Kraaimaat F, Bijlsma J. Development of a self-report questionnaire to assess the impact of rheumatic disease on health and lifestyle. *J Rehab Sci* 1990;3:65–70.
34. Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcomes* 2003;1:29.
35. Spinhoven P, Ormel J, Sloekers PP, *et al*. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997;27:363–70.
36. Sanderman R, Ormel J. De Utrechtse Coping Lijst (UCL): validiteit en betrouwbaarheid [The Utrecht Coping List (UCL): validity and reliability]. *Gedrag en Gezondheid* 1992;20:32–7.
37. Evers AW, Taal E, Kraaimaat FW, *et al*. A comparison of two recently developed health status instruments for patients with arthritis: Dutch-AIMS2 and IRGL. *Br J Rheumatol* 1998;37:157–64.
38. Schunck R, Perales F. Within- and between-cluster effects in generalized linear mixed models: A discussion of approaches and the xthybrid command. *The Stata Journal* 2017;17:89–115.
39. Curran PJ, Bauer DJ. The disaggregation of within-person and between-person effects in longitudinal models of change. *Annu Rev Psychol* 2011;62:583–619.
40. Twisk J, Rijmen F. Longitudinal tobit regression: a new approach to analyze outcome variables with floor or ceiling effects. *J Clin Epidemiol* 2009;62:953–8.
41. Sturgeon JA, Finan PH, Zautra AJ. Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. *Nat Rev Rheumatol* 2016;12:532–42.
42. Müller R, Kull M, Põlluste K, *et al*. The metabolic profile in early rheumatoid arthritis: a high prevalence of metabolic obesity. *Rheumatol Int* 2017;37:21–7.
43. Di Giuseppe D, Bottai M, Askling J, *et al*. Physical activity and risk of rheumatoid arthritis in women: a population-based prospective study. *Arthritis Res Ther* 2015;17:40.
44. Hu Y, Sparks JA, Malspeis S, *et al*. Long-term dietary quality and risk of developing rheumatoid arthritis in women. *Ann Rheum Dis* 2017;76:1357–64.
45. Lahiri M, Luben RN, Morgan C, *et al*. Using lifestyle factors to identify individuals at higher risk of inflammatory polyarthritis (results from the European Prospective Investigation of Cancer-Norfolk and

the Norfolk Arthritis Register–the EPIC-2-NOAR Study). *Ann Rheum Dis* 2014;73:219–26.

46. Vermeulen-Smit E, Ten Have M, Van Laar M, *et al*. Clustering of health risk behaviours and the relationship with mental disorders. *J Affect Disord* 2015;171:111–9.

47. Matcham F, Davies R, Hotopf M, *et al*. The relationship between depression and biologic treatment response in rheumatoid arthritis: An analysis of the British Society for Rheumatology Biologics Register. *Rheumatology* 2018;57:835–43.

48. van Beers-Tas MH, Turk SA, van Schaardenburg D. How does established rheumatoid arthritis develop, and are there possibilities for prevention? *Best Pract Res Clin Rheumatol* 2015;29:527–42.

49. Stack RJ, Sahni M, Mallen CD, *et al*. Symptom complexes at the earliest phases of rheumatoid arthritis: a synthesis of the qualitative literature. *Arthritis Care Res* 2013;65:1916–26.

50. van Tuyl LH, Stack RJ, Sloots M, *et al*. Impact of Symptoms on Daily Life in People at Risk of Rheumatoid Arthritis. *Musculoskeletal Care* 2016;14:169–73.