

# Longterm Predictors of Anxiety and Depressed Mood in Early Rheumatoid Arthritis: A 3 and 5 Year Followup

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**ABSTRACT. Objective.** Heightened levels of anxiety and depressed mood are known to be common consequences of rheumatoid arthritis (RA). We examined the role of stress vulnerability factors in the longterm course of anxiety and depressed mood in patients with early RA. Specifically, the role of personality characteristics (neuroticism, extraversion), physical and psychological stressors (clinical status, disease influence on daily life, major life events), and coping and social support at the time of diagnosis were studied to predict changes in anxiety and depressed mood 3 and 5 years later.

**Methods.** Anxiety and depressed mood, predicted from clinical and self-reported assessments of stress vulnerability factors at the time of diagnosis in 78 patients with RA were assessed again after 3 and 5 years.

**Results.** A worse clinical status, more neuroticism, and lower education level at the time of diagnosis were all significantly related to increased psychological distress at the 3 and 5 year followup. However, the personality characteristics of neuroticism proved to be the most consistent and effective predictor of anxiety and depressed mood after 3 and 5 years, irrespective of initial distress levels, biomedical factors, use of medication, and other stressors or vulnerability factors.

**Conclusion.** Results indicate the prognostic value of personality characteristics for longterm susceptibility to distress in patients with early RA, and emphasize the importance of paying close attention to factors unrelated to RA when screening for patients at risk. (J Rheumatol 2002;29:2327–36)

## Key Indexing Terms:

RHEUMATOID ARTHRITIS  
ANXIETY

DEPRESSED MOOD

QUALITY OF LIFE  
NEUROTICISM

The diagnosis of a chronic, disabling disease such as rheumatoid arthritis (RA) can have a significant impact on an individual's daily life, since patients have to deal with a potentially uncontrollable, unpredictable, longterm condition that may affect almost all aspects of their physical, psychological, and social functioning<sup>1,2</sup>. Although most patients seem to adjust well to the changes imposed by the disease and find an acceptable level of well being, about 20% suffer heightened levels of anxiety and depression, comparable to those of people with anxiety and depressive

disorders<sup>3-7</sup>. To understand the individual variability in psychological adjustment to RA, research has focused on identifying risk factors for patients for whom the confrontation with the chronic disease seems to exceed their adaptive capacities and who become highly distressed.

On the basis of stress vulnerability models<sup>8-11</sup>, different stressors and vulnerability factors have been proposed to affect distress levels in patients with RA. For example, chronic, disease related stressors such as a worse clinical status due to more disease activity, pain, and functional disability, and the psychological impact of the disease on daily life due to limited possibilities in daily activities or changes in social relationships have been shown to affect anxiety and depression in patients with RA<sup>12-15</sup>. Further, major stressful life events are known to be important predictors of longterm distress in the general population<sup>16,17</sup> and may similarly affect distress in patients with RA<sup>18-20</sup>. Regarding vulnerability factors, the manner of coping with stress and the level of social support have been shown to have an effect on well being in patients with RA and direct, mediating, or moderating effects on the stress-illness relationship. Based on general distinctions between active, problem focused coping and passive, avoidant coping, it has repeatedly been found that the use of more passive coping strategies is prospectively related to heightened distress in

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Supported in part by grants from the Dutch League Against Rheumatism ("Nationaal Reumafonds").

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Submitted August 13, 2001; revision accepted April 15, 2002.

RA<sup>21-24</sup>. Similarly, patients with RA with less social support — in terms of the quantity, i.e., the size of their social network, as well as the quality, i.e., the perceived availability of support — have been shown to adjust less successfully to their chronic condition<sup>7,19,25</sup>. Attention has also been directed to the influence of relatively stable personality characteristics as vulnerability factors for maladjustment in patients with RA<sup>26,27</sup>. Two dimensions in particular, neuroticism, the tendency to be relatively more tense and emotionally unstable, and extraversion, the tendency to be relatively more sociable and impulsive, are related to health and well being in various chronic diseases, including RA<sup>26-30</sup>. In addition, personality characteristics are assumed to be crucial in accounting for the effects of stressors, coping, and social support on longterm distress, since people with high neuroticism and low extraversion report more physical complaints and stressful life events, experience less social support, and engage in more dysfunctional coping behavior<sup>26-33</sup>.

So far, empirical evidence supports a link between stress vulnerability factors and psychological distress in patients with RA. However, definite conclusions about the specific kinds of variables and their relative contributions cannot be drawn from present research, since a comprehensive test of various stressors and vulnerability factors has rarely been conducted. In addition, patients have usually been followed for relatively short periods of time in prospective studies, and the extent to which the kinds of predictors and strength and direction of effects for short term outcomes can be generalized to longterm outcomes is largely unknown<sup>34</sup>. Moreover, stressors and vulnerability factors have usually been assessed in patients with long-standing RA. Stress-vulnerability factors are known to be affected by the disease process, its biopsychosocial consequences, and pharmacological treatment<sup>1,2,14,35,36</sup>, and they may consequently be more validly assessed in recently diagnosed patients. In addition, an identification of stress vulnerability factors in recently diagnosed patients may allow patients to be screened at the earliest possible time after contacting a rheumatologist, at diagnosis.

We investigated the predictive value of a comprehensive set of stress vulnerability factors at the time of diagnosis for the longterm course of psychological distress in early RA. The role of stress vulnerability factors at the time of diagnosis has previously been studied by our group, to predict psychological distress in the first year after diagnosis<sup>7</sup>. However, stressors and vulnerability factors scarcely predicted the course of distress in the first year after diagnosis. In this study, followup results after 3 and 5 years are presented. Specifically, the role of personality characteristics (neuroticism, extraversion), stressors (clinical status, disease impact on daily life, major life events), coping, and social support at the time of diagnosis was studied to predict anxiety and depressed mood 3 and 5 years later. It was expected that more neuroticism and less extraversion, higher

levels of stressors, greater use of passive coping, and less use of active coping as well as less social support would predict an increase in psychological distress after 3 and 5 years. We further examined whether stressors, coping, and social support account for the effects of personality characteristics on longterm psychological distress (mediating effects of stressors, coping, and social support). Finally, we explored whether the maladaptive effects of stressors on psychological distress might be increased in patients with more unfavorable vulnerability factors (moderating effects of personality characteristics, coping, and social support on stressors).

## MATERIALS AND METHODS

*Sample and procedure.* The study sample consisted of outpatients with recently diagnosed RA from 5 hospitals in the Utrecht area of the Netherlands. All patients participated in one of 2 medical trials of second-line antirheumatic drugs<sup>36,37</sup>. Inclusion criteria for the medical trials were a minimum age of 18 years, diagnosis according to the 1987 American College of Rheumatology (ACR) criteria<sup>38</sup>, and a duration of disease of less than one year. Exclusion criteria were comorbid conditions that might interfere with one of the medication strategies (such as malignancy, cardiac, respiratory, hepatic, and renal insufficiency), previous or current treatment with second-line antirheumatic drugs, use of glucocorticoids, cytotoxic or immunosuppressive drugs, possible pregnancy or breast feeding, and psychiatric or mental disturbances that severely interfere with adherence to the study protocol. All incoming patients from the hospitals who met the inclusion criteria were asked to participate in the medical trials. About 25% of the patients did not agree to be randomized, but there were no differences found between these patients and participants in terms of their levels of disease activity. From the remaining 394 patients participating in the medical trials, a subgroup of 100 patients were randomly selected for participation in the present study.

Patients were informed about this study by their rheumatologists during their first visit, when ACR criteria were assessed. About 3 weeks later (range 0–12 weeks), clinical and self-report data were assessed during their second visit. This second visit was also the starting point for the prospective medical trials. Five patients did not return the questionnaires at this assessment point, resulting in 95 patients who participated in the study at the time of diagnosis. In addition to assessing clinical and self-report data at the beginning of the study and at the one year followup<sup>7</sup>, data on disease activity, functional disability, pain, and psychological distress were again collected at the 3 and 5 year followups.

Of the 95 patients who correctly completed self-report data at the first assessment, 78 (82%) completed all assessment points during the 5 year study period. Participants in the followup were predominantly female (69%), married or living with a partner (76%), and had a primary (32%) or secondary (57%) education level. Mean age at the time of entering the study was 57 years (range 20–82). In terms of dropouts, 7 patients died, 2 moved, one was in remission and no longer treated in the rheumatology outpatient clinic, and 7 did not complete the questionnaires for the followup assessments. When entering the study, dropouts did not significantly differ from participants in terms of demographic variables (sex, age, marital status, education level), disease activity, pain, functional disability, disease impact on daily life, experience of major life events, personality dimensions of extraversion, coping, or social support. However, dropouts scored higher on both indicators of psychological distress ( $t = 2.61$ ,  $p < 0.05$  for anxiety and  $t = 2.24$ ,  $p < 0.05$  for depressed mood) and on the personality dimension of neuroticism ( $t = 2.87$ ,  $p < .01$ ) than patients who completed all assessment points.

When included in the medication trials, all patients were randomly assigned to one of the medication strategies. The drug trials lasted at least 2 years for all patients, but medication strategies were continued unless

adverse reactions or ineffectiveness made discontinuation inevitable in the opinion of the attending doctor. In that case, one of the other medication strategies from the trials was usually prescribed. The distribution of medication strategies was as follows: 30% and 23% of patients used non-steroidal antiinflammatory drugs (NSAID) alone at first assessment and at the 5 year followup, respectively; the other patients took NSAID in combination with methotrexate (MTX; 30% and 49%, respectively), intramuscular gold (14% at both assessment points), hydroxychloroquine (HCQ; 15% and 9%), prednisone (11% and 1%), or other second-line medication, prescribed only for individual patients (4% at the 5 year followup). At the 5 year followup, 31% of the patients still used the initially prescribed medication (6% NSAID alone, 17% MTX, 4% intramuscular gold, 3% HCQ, and 1% prednisone), while 65% used another medication strategy from the drug trial (17% NSAID alone, 32% MTX, 10% intramuscular gold, 6% HCQ), and 4% of the patients used another second-line medication than those used in the medication trials. Finally, no patient in the psychosocial study met removal criteria during the study period, i.e., the occurrence of other serious disease processes or an incorrect RA diagnosis. *Measures.* Demographic variables were assessed with a general checklist for patients' sex (0:M, 1:F), age, and marital status (0: unmarried, 1: married). In addition, education level was measured using 7 categories that can be classified as primary, secondary, and tertiary education levels, representing on average 7, 12, and 17 years of education, respectively.

Disease activity was determined by erythrocyte sedimentation rate (ESR; 1–140 mm/h) and by Thompson's joint score ratings of the simultaneous presence of swelling and pain in 38 joints<sup>39</sup>. A composite score of both variables was used, in accord with regular use of composite scores of disease activity that consist of at least ESR or another acute phase reactant and a joint score (e.g., the modified Disease Activity Score<sup>40</sup>). The composite score was calculated by adding the standardized scores (z scores) of both indicators.

Functional disability was assessed using a composite score of one clinical measure and 2 self-report measures<sup>41</sup>. The clinical measure consisted of grip strength assessments with a Martin vigorimeter (the mean of 3 measurements on both hands was calculated). Self-reported functional disability was assessed with the mobility and self-care scales of the Impact of Rheumatic Diseases on General Health and Lifestyle instrument (IRGL)<sup>42,43</sup>, a questionnaire derived from the Arthritis Impact Measurement Scales (AIMS)<sup>44</sup>, which assesses physical, psychological, and social health in patients with rheumatic diseases. Research has shown that the reliability and validity of the IRGL scales are highly satisfactory<sup>42,43</sup>. The mobility and self-care scales, which assess the functional capacities of the lower and upper extremities, respectively, over the last month (15 items) have been shown to be highly comparable to the AIMS physical functioning scales<sup>43</sup>. Cronbach's alpha in this study was 0.89 for both scales. A composite score of the clinical measure of grip strength and the 2 mobility and self-care self-report scales was calculated by adding the standardized scores (z scores) of all 3 indicators. A higher composite score indicates higher levels of functional disability.

Pain was assessed with the IRGL pain scale (6 items), measuring the severity and frequency of painful episodes and swollen joints and duration of early morning stiffness in the last month. Cronbach's alpha in this study was 0.88.

Psychological distress was measured with the IRGL anxiety and depressed mood scales. The anxiety scale is a shortened version of the Dutch State Anxiety Scale (10 items)<sup>45,46</sup>, assessing anxiety levels in the last month. The depressed mood scale (6 items) is derived from Zwart and Spooen's questionnaire<sup>47</sup> and assesses various depressed mood states over the previous 2 weeks. Cronbach's alpha for the anxiety and depressed mood scales in this study were 0.91 and 0.94, respectively.

Disease impact on daily life was measured with the IRGL disease impact scale (10 items), which assesses the general influence of the disease on several areas of daily life (i.e., work, leisure, relationships, sexuality, eating). Cronbach's alpha in the present study was 0.87.

Major life events were measured with a Dutch version of the Life

Experience Survey (LES), assessing the occurrence of 60 stressful events related to health, work, financial circumstances, relationships, living, and personal matters in the last 12 months<sup>48,49</sup>. To minimize confounding effects between major life events and disease impact on daily life, 4 disease related events were excluded (occurrence of severe disease, important changes in health status, hospital admission, surgery).

Personality dimensions, i.e., neuroticism and extraversion, were measured with a Dutch version of the Eysenck Personality Questionnaire (EPQ)<sup>50,51</sup>. Cronbach's alpha in this study was 0.90 for neuroticism and 0.79 for extraversion.

Coping strategies were assessed with the Utrecht Coping List (UCL)<sup>52</sup>, a well documented coping questionnaire used in the Netherlands<sup>7,24</sup>, adapted from Westbrook<sup>53</sup>, which measures on a 4 point Likert scale active and passive coping strategies when dealing with everyday problems. Active coping was assessed with the problem focusing scale (7 items), measuring cognitive and behavioral efforts to apply goal oriented problem-solving strategies. Passive coping was measured with the avoidance scale (8 items), measuring cognitive and behavioral attempts to avoid, escape from, and acquiesce when facing everyday problems. Cronbach's alpha in the study was 0.85 for the active and 0.67 for the passive coping scales.

Social support in the past 6 months was measured with the IRGL social functioning scales, reflecting a quantitative and qualitative aspect of social support. The quantitative aspect was assessed by the size of the social network, i.e., the number of friends and family members with whom patients associate. The qualitative aspect was measured with the perceived support scale (5 items), inquiring about perceived availability of emotional and instrumental support. Cronbach's alpha for the perceived support scale was 0.88.

*Statistical analyses.* The number of patients scoring on anxiety and depressed mood equal to or higher than mean scores of psychiatric outpatients and patients with a clinical anxiety and depression diagnosis was determined by comparing scores to mean scores of representative norm groups in Dutch populations of psychiatric outpatients and patients with a clinical anxiety or depression diagnosis<sup>46,47</sup>. To study mean linear changes in clinical status and psychological distress over time, a general linear model with repeated measurements was applied for every indicator of clinical status (disease activity, functional disability, pain) and psychological distress (anxiety and depressed mood), using the variables at the different assessment points as dependent variables, followed by post-hoc tests in the case of significant linear changes.

To explore the relationship between stress vulnerability factors at the time of diagnosis and changes in anxiety and depressed mood after 3 and 5 years, Pearson correlation coefficients were calculated between the stress vulnerability factors at first assessment and the change scores of anxiety and depressed mood at the 3 and 5 year followup. Residual gain scores were used to measure changes in anxiety and depressed mood<sup>54</sup>. Residual gain scores take into account the individual baseline levels and control for regression to the mean effects. Residual gain scores were calculated by regressing the outcome variable at the followup assessment (e.g., depressed mood at the 3 year followup) on the baseline score of the outcome measure (e.g., depressed mood at the time of diagnosis). Sequential regression analyses were then performed to study the relative contribution of the stress vulnerability factors to anxiety and depressed mood at the 3 and 5 year followup. Anxiety and depressed mood at the 3 and 5 year followup were used as dependent variables. In the first step, anxiety and depressed mood assessed at the time of diagnosis were entered, reflecting residual gain scores. In the following steps, the different predictors were entered that were significantly related to the residual gain scores of anxiety and depressed mood at at least one followup assessment. These predictors were entered in consecutive steps in the regression analyses to test their additional contribution in terms of significant F-change, after taking into account the variance explained by the other predictors. The grouping of variables in a step as well as the entry order of the steps was determined *a priori* by the stress vulnerability model (e.g., indicators of clinical status were entered in one step together, and they were entered after the more

stable characteristics of demographic variables and personality characteristics). However, entry order between steps was also changed to study the single contribution of every step, above the variance already explained by the baseline scores of anxiety and depressed mood. The strength of the beta (standardized regression coefficients) and the accompanying t test were used as an indicator of the relative contribution of a predictor in comparison to all other predictors that are tested in the model, independent of entry order.

Possible mediating effects were determined according to the procedure described by Baron and Kenny<sup>55</sup>: when both a predictor and a possible mediator explain significant variance in a dependent variable, the mediator is entered before the predictor in the sequential regression analyses to reveal whether the predictor does not any longer explain significant variance, when taking the influence of the mediator into account. Moderating effects were explored by entering centered interaction terms between the predictor and the moderator in the regression analyses, after controlling for their main effects. Due to the relatively large number of explorative tests performed in these analyses, a more conservative threshold of  $p < 0.001$  was used. To control for possible confounding effects of medication, Pearson correlation coefficients were calculated between the use and duration of every medication strategy prescribed at the time of diagnosis and changes in anxiety and depressed mood at the 3 and 5 year followup. In the event of a significant correlation, the effects of the medication strategy was taken into account by entering the medication strategy at step 2 before the stress vulnerability factors in the regression analyses. Statistical analyses were all conducted with SPSS/Windows 9.0 with a minimum of 76 patients sharing complete data sets.

## RESULTS

*Clinical and psychological health status during the study period.* Levels of clinical status (disease activity, functional disability, and pain) and psychological distress (anxiety and depressed mood) when entering the study were comparable to those previously reported in representative samples with

recent or long-standing RA<sup>42,43,56</sup> (see Table 1 for means and SD of clinical status and psychological distress levels during the study period).

During the 5 year period, there was a significant improvement in clinical status. Both indicators of disease activity, pain and one of the functional disability measures, grip strength, significantly decreased within 5 years after diagnosis [F(3,73) = 22.2,  $p < 0.001$  for ESR; F(3,73) = 10.6,  $p < 0.01$  for the joint score; F(3,75) = 9.6,  $p < 0.01$  for pain; F(3,75) = 14.5,  $p < 0.001$  for grip strength]. Post hoc tests indicated that this improvement in clinical status was most obvious in the first year of the disease: all indicators decreased in this year ( $t = 3.06$ ,  $p < 0.01$  for ESR;  $t = 3.25$ ,  $p < 0.01$  for the joint score;  $t = 2.20$ ,  $p < 0.05$  for pain;  $t = 4.29$ ,  $p < 0.001$  for grip strength)<sup>7</sup>, possibly due to the beneficial effects of medication<sup>36,37</sup>. After the first year of the disease, clinical status remained relatively stable, as indicated by nonsignificant post hoc tests between 1 and 3 years and between 3 and 5 years, with one exception: ESR significantly decreased further between 1 and 3 year followup ( $t = 3.11$ ,  $p < 0.01$ ), but not between 3 and 5 year followup. In contrast to the considerable improvement in clinical status, mean psychological distress remained relatively stable during the study period. Although an overall decrease was found for anxiety during the 5 year study period [F(3,73) = 4.37,  $p < 0.05$ ], post hoc tests between the different assessment points were all nonsignificant. In addition, depressed mood did not change significantly during the study period.

Examining risk groups for psychological distress at the

Table 1. Means and standard deviations of clinical and psychological health status at the time of diagnosis and at the 1, 3, and 5 year followup in 78 patients with RA.

Disease Activity and Pain	ESR	Joint Score	Pain
	Mean (SD)	Mean (SD)	Mean (SD)
At diagnosis	29.4 (22.3)	97.5 (100.7)	15.8 (4.9)
1 yr followup	23.6 (22.4)	66.7 (75.7)	14.6 (5.4)
3 yr followup	17.7 (13.2)	63.4 (90.4)	14.0 (5.6)
5 yr followup	20.0 (14.7)	73.1 (110.6)	13.7 (5.3)
Functional Disability <sup>†</sup>	Grip Strength	Mobility	Self-care
	Mean (SD)	Mean (SD)	Mean (SD)
At diagnosis	32.2 (22.0)	19.5 (6.1)	24.2 (5.9)
1 yr followup	40.2 (26.0)	21.1 (5.8)	25.1 (5.7)
3 yr followup	43.1 (24.4)	20.9 (6.4)	25.9 (6.1)
5 yr followup	41.9 (24.8)	20.3 (6.6)	25.1 (6.5)
Psychological Distress	Anxiety	Depressed Mood	
	Mean (SD)	Mean (SD)	
At diagnosis	18.75 (6.23)	3.72 (4.76)	
1 yr followup	18.75 (6.91)	3.16 (4.15)	
3 yr followup	18.07 (5.39)	3.32 (4.08)	
5 yr followup	17.46 (6.16)	2.84 (4.08)	

<sup>†</sup> Lower levels of grip strength, mobility, and self-care indicate higher levels of functional disability.

Table 2. Correlations at the time of diagnosis.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Demographic variables																
1. Age																
2. Sex	0.08															
3. Education level	-0.40***	-0.31**														
4. Marital status,	-0.03	-0.18	0.09													
Personality characteristics																
5. Neuroticism	0.00	0.21	-0.11	-0.12												
6. Extraversion	-0.13	-0.15	0.01	0.10	-0.35**											
Clinical status																
7. Disease activity	-0.16	0.18	0.02	0.00	0.18	0.00										
8. Functional disability	0.07	0.38**	-0.11	0.05	0.37***	-0.03	0.46***									
9. Pain	-0.26*	-0.14	0.17	0.10	0.14	0.04	0.45***	0.21								
Psychological stressors																
10. Disease impact	-0.03	0.20	-0.05	-0.21	0.43***	-0.15	0.30**	0.41***	0.32**							
11. Major life events	-0.28*	-0.06	0.31**	0.00	0.34**	0.01	0.02	0.02	0.22	0.22						
Coping																
12. Active problem-focusing	-0.33*	-0.32**	0.44***	0.14	-0.18	0.26*	-0.05	-0.25*	0.08	-0.12	0.22					
13. Passive avoidance	0.10	0.13	-0.02	-0.06	0.32**	-0.23*	0.13	0.01	0.19	0.11	0.05	0.06				
Social support																
14. Social network	-0.08	-0.30*	0.13	0.14	-0.18	0.24*	0.12	-0.16	0.00	-0.08	-0.12	0.26*	0.08			
15. Perceived support	-0.16	-0.10	0.10	0.16	-0.17	0.03	0.04	-0.02	0.03	-0.02	-0.19	0.24*	-0.02	0.26*		
Psychological distress																
16. Anxiety	0.00	0.25*	-0.03	-0.20	0.74***	-0.40***	0.16	0.26*	0.30**	0.55***	0.40***	-0.11	0.28*	-0.28*	-0.24*	
17. Depressed mood	0.04	0.13	-0.10	-0.14	0.64***	-0.31**	0.19	0.17	0.43***	0.51***	0.20	-0.18	0.25*	-0.24*	-0.22*	0.75***

\* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001.

different assessment points, 32–39% and 18–26% of the patients scored equal to or higher than the mean scores of psychiatric outpatients on depressed mood and anxiety, respectively, while 17–21% and 12–21% scored equal to or higher than the mean scores of patients with a clinical depression or anxiety diagnosis, respectively<sup>46,47</sup>.

*Predictors of anxiety and depressed mood at 3 and 5 year followup.* Correlations between stress vulnerability factors at the time of diagnosis and change of anxiety and depressed mood at the 3 and 5 year followup are presented in Table 3. Results indicated that the personality dimension of neuroticism was significantly related to an increase in depressed mood at both assessment points and an increase in anxiety at the 5 year followup. Moreover, a worse clinical status was related to an increase in psychological distress: higher levels of disease activity and functional disability were associated with an increase in anxiety at the 5 year followup, and higher levels of functional disability were related to an increase in depressed mood at the 3 and 5 year followup. Nonsignificant correlations were revealed between changes in anxiety and depressed mood at both assessment points and the initial assessment of extraversion, pain, disease impact on daily life, major life events, coping, and social support. In addition, demographic variables of age, sex, and marital status were not related to changes in anxiety or depressed mood at followup assessments. However, lower

education level was significantly related to an increase in anxiety and depressed mood at the 5 year, but not at the 3 year followup.

Multiple regression analyses were then performed to study the relative contribution of the stress vulnerability factors for longterm changes in psychological distress. Anxiety and depressed mood at the 3 and 5 year followup were used as dependent variables. In the first step, the initial assessments of anxiety and depressed mood at the time of diagnosis were entered, followed by the stress vulnerability factors that were significantly related to changes in anxiety or depressed mood at at least one assessment point: education level, neuroticism, and 2 indicators of clinical status (disease activity and functional disability), all measured at the time of diagnosis. As Table 4 reveals, results showed that lower education level significantly predicted anxiety at the 3 and 5 year followup and depressed mood at the 5 year followup (F-change = 4.80, p < 0.05, and F-change = 10.00, p < 0.01 for anxiety at the 3 and 5 year followup, respectively; F-change = 5.71, p < 0.05 for depressed mood at the 5 year followup), after taking into account the effects of initial levels of psychological distress in the first step (F-change = 54.32, p < 0.001 and F-change = 31.04, p < 0.001 for anxiety at the 3 and 5 year followup, respectively; F-change = 44.61, p < 0.001 and F-change = 23.10, p < 0.001 for depressed mood at the 3 and 5 year followup, respec-

**Table 3.** Correlations between stress vulnerability factors at the time of diagnosis and change in anxiety and depressed mood after 3 and 5 years. Positive scores indicate that stress vulnerability factors are related to an increase in anxiety and depressed mood. Stress vulnerability factors significantly related to anxiety or depressed mood at least one assessment point are printed in bold type.

	Change in Anxiety		Change in Depressed Mood	
	3 yrs	5 yrs	3 yrs	5 yrs
Demographic variables				
Age	0.06	0.12	0.03	0.12
Sex	0.04	0.09	0.17	0.13
<b>Education level</b>	<b>-0.22</b>	<b>-0.34**</b>	<b>-0.17</b>	<b>-0.27*</b>
Marital status	0.02	0.02	0.06	0.05
Personality characteristics				
<b>Neuroticism</b>	<b>0.20</b>	<b>0.27*</b>	<b>0.39**</b>	<b>0.33**</b>
Extraversion	-0.07	-0.05	-0.08	-0.10
Clinical status				
<b>Disease activity</b>	<b>0.11</b>	<b>0.23*</b>	<b>0.18</b>	<b>0.19</b>
<b>Functional disability</b>	<b>0.20</b>	<b>0.28*</b>	<b>0.25*</b>	<b>0.28*</b>
Pain	0.10	-0.09	-0.04	-0.04
Psychological stressors				
Disease impact	0.15	0.00	0.17	0.18
Major life events	-0.12	-0.07	0.09	0.09
Coping				
Active problem-focusing	-0.11	-0.10	0.08	-0.11
Passive avoidance	0.12	0.10	0.21	0.03
Social support				
Social network	-0.08	-0.08	-0.04	-0.06
Perceived support	0.10	0.00	0.02	-0.07

\* p < 0.05, \*\* p < 0.01.

**Table 4.** Multiple regression analyses predicting anxiety and depressed mood at the 3 and 5 year followup from stress vulnerability factors at the time of diagnosis. Selection criterion for the inclusion of stress vulnerability factors in the regression analyses was a significant correlation with changes in psychological distress at at least one followup assessment point (Table 3).

	Anxiety				Depressed Mood			
	3 yrs		5 yrs		3 yrs		5 yrs	
	$\beta^\dagger$	$\Delta R^{2\dagger\dagger}$	$\beta$	$\Delta R^2$	$\beta$	$\Delta R^2$	$\beta$	$\Delta R^2$
Psychological distress								
Anxiety	0.44**	0.42**	0.21	0.30**				
Depressed mood					0.26*	0.38**	0.15	0.24**
Demographic variables								
Education level	-0.16	0.04*	-0.24**	0.08**	-0.10	0.01	-0.21*	0.05*
Personality characteristics								
Neuroticism	0.24	0.03*	0.37**	0.08**	0.48***	0.14***	0.42**	0.12***
Clinical status								
Disease activity	0.03	0.01	0.14	0.04	0.12	0.02	0.13	0.02
Functional disability	0.08		0.10		-0.01		-0.06	
Total $\Delta R^2$		0.50***		0.50***		0.55***		0.43***

$\dagger$  Probability level of t test.  $\dagger\dagger$  Probability level of F-change. \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001.

tively). Neuroticism at step 3 explained significant additional variance to anxiety and depressed mood at the 3 and 5 year followup (F-change = 4.45, p < 0.05 and F-change = 10.28, p < 0.01 for anxiety at the 3 and 5 year followup, respectively; F-change = 20.90, p < 0.001 and F-change = 13.87, p < 0.001 for depressed mood at the 3 and 5 year

followup, respectively), while clinical status at step 4 failed to predict additional variance in both measures of psychological distress. As shown in Table 4, beta coefficients for the full regression equation showed that lower education level significantly predicted more anxiety and depressed mood at the 5 year followup (t = -2.83; p < 0.01 and t =

-2.27,  $p < 0.05$ , respectively). However, neuroticism proved to be the better predictor for depressed mood at the 3 and 5 year followup ( $t = 4.19$ ,  $p < 0.001$  and  $t = 3.26$ ,  $p < 0.01$ , respectively) as well as for anxiety at the 5 year followup ( $t = 2.77$ ,  $p < 0.01$ ). In addition, neuroticism tended towards significance in the prediction of anxiety at the 3 year followup ( $t = 1.77$ ,  $p = 0.08$ ).

Results were very similar when the entry order of predictor variables was changed. Education level and neuroticism significantly predicted the same indicators of psychological distress, independently of entry order, except that education level only tended to predict anxiety at the 3 year followup, when entered after neuroticism or clinical status at step 3 or 4 (F-change = 3.55,  $p = 0.06$  at step 3 and F-change = 3.28,  $p = 0.07$  at step 4). Similarly, when entering clinical status at step 2 or 3 in the regression analyses (before education level or neuroticism), it still failed to predict significant variance in anxiety at the 3 year followup and depressed mood at the 3 and 5 year followup. However, clinical status significantly predicted anxiety at the 5 year followup, when entered at step 2 or 3 (F-change = 3.98,  $p < 0.05$  at step 2 and F-change = 3.79,  $p < 0.05$  at step 3), indicating that education level and neuroticism both accounted for the relationship between clinical status and anxiety at the 5 year followup. Separate analyses for both indicators of clinical status showed that neuroticism and education level only explained the variance of functional disability to anxiety at the 5 year followup. The effect of disease activity on anxiety at the 5 year followup still remained significant taking into account the effects of education level and neuroticism (F-change = 4.27,  $p < 0.05$ ), indicating that disease activity was an additional independent predictor of anxiety at the 5 year followup.

Moderator effects were then explored by entering centered interaction terms between all stressors and vulnerability factors in the regression analyses, after controlling for their main effects. Results indicated that none of the interaction terms predicted anxiety or depressed mood at the 3 and 5 year followup.

*Confounding effects of medication.* Correlations between the medication strategies prescribed at the time of diagnosis (NSAID alone, NSAID in combination with MTX, intramuscular gold, HCQ, or prednisone) and changes in anxiety and depressed mood at the 3 and 5 year followup indicated that the use and duration of the various medication strategies were not significantly related to changes in anxiety at the 3 and 5 year followup or to changes in depressed mood at the 5 year followup. The only significant associations were those between 2 medication strategies and changes in depressed mood at the 3 year followup: the use and duration of intake of hydroxychloroquine were related to an increase, and the use and duration of intake of prednisone were related to a decrease of depressed mood at the 3 year followup ( $r = 0.33$ ,  $p < 0.01$  and  $r = 0.37$ ,  $p < 0.001$  for the

use and duration of hydroxychloroquine, respectively;  $r = -0.29$ ,  $p < 0.05$  and  $r = -0.29$ ,  $p < 0.05$  for the use and duration of prednisone, respectively). However, when controlling for these variables in the regression analysis (Table 4) by entering these medication strategies at step 2 in the regression analyses, neuroticism still significantly predicted depressed mood at the 3 year followup (F-change = 11.75,  $p < 0.001$ ), after controlling for the baseline levels of depressed mood (F-change = 42.52,  $p < 0.001$ ) and the effects of the medication strategies (F-change = 4.29,  $p < 0.01$ ). In addition, beta coefficients indicated that neuroticism remained the best predictor of depressed mood at the 3 year followup (beta = 0.41;  $t = 3.48$ ,  $p < 0.001$ ) together with the only other significant predictor, the baseline level of depressed mood (beta = 0.32,  $t = 2.84$ ,  $p < 0.01$ ).

## DISCUSSION

A comprehensive set of stressors and vulnerability factors was examined at the time of diagnosis for its ability to predict longterm anxiety and depressed mood in patients with RA. Results revealed that a worse clinical status, more neuroticism, and lower education level at the time of diagnosis were all related to an increase in indicators of psychological distress after 3 and 5 years, demonstrating that both disease related stressors and psychosocial vulnerability factors can affect longterm distress in patients with early RA. However, neuroticism proved to be the most consistent and effective predictor, reflecting that this relatively stable personality dimension has the best prognostic value for longterm distress susceptibility in patients, irrespective of biomedical variables, use of medication, or other stressors and vulnerability factors.

The predictive value of neuroticism for future distress levels is well documented in the general population<sup>57</sup>. Neuroticism also prospectively predicted daily mood disturbances in patients with RA<sup>26</sup>, suggesting, together with our findings, that this relatively stable personality characteristic has prognostic value for short and longterm psychological distress in patients with RA. Independently from neuroticism, a lower level of education predicted anxiety at 3 and 5 year followup and depressed mood at the 5 year followup. As for neuroticism, the prognostic value of lower socioeconomic status on future distress is well established in the general population<sup>58</sup> and concurrent and prospective links have also been reported in patients with RA<sup>12,59,60</sup>. Irrespective of whether individuals are confronted with a longterm chronic condition, such as RA, distress levels seem to be similarly affected by the relatively stable personality characteristic of neuroticism and education level. In contrast, the relationship of clinical status to future distress did not remain significant in regression analyses, except for anxiety levels at the 5 year followup. Detailed analyses also revealed that both neuroticism and education level accounted for the relationship of functional disability to

anxiety at the 5 year followup, but not that of disease activity to anxiety at the 5 year followup. These results are in accord with previous findings showing that individuals with higher neuroticism scores and lower education levels are more disabled and complain more about physical symptoms, while their biomedical status of disease activity is about the same<sup>31,32,59,60</sup>. Consequently, reasons other than RA disease activity, such as a lack of health behaviors and perceptions of control or more selective processing of bodily signals<sup>60-62</sup>, may account for the relationship between the physical symptoms reported and future distress. Together, these findings strongly suggest that RA itself has relatively little, if any, effect on the longterm course of psychological distress, and whether individuals become more depressed or anxious in the long run is determined by relatively general and stable vulnerability factors.

Although vulnerability factors for psychological distress found in our study seem to correspond closely to those in the general and psychiatric populations, this does not necessarily imply that neuroticism and education level act in the same way in patients with RA as in controls. Indeed, research has revealed specific, disease related mediators in patients with RA for both vulnerability factors. For example, the relationship between lower education level and mortality rates in patients with RA has been shown to be mediated by an attitude of helplessness toward the disease<sup>63</sup>, while the relationship of neuroticism to future pain reports could be explained by the tendency of patients to catastrophize when faced with pain<sup>26</sup>. These findings suggest that links of neuroticism and education level to future outcomes might be differently determined in patients with RA than in the general population, at least with regard to physical outcomes. Perhaps even more important, these results also indicate that their effects are mediated by actual cognitive and behavioral responses to the disease, which can be modified by psychosocial interventions. It may be crucial in future research to specify the physiological, cognitive-emotional, behavioral, and social mechanisms, in terms of how these factors operate when people are faced with a chronic disease and how they affect RA patients' physical and psychological outcomes.

Investigating stress vulnerability factors at the time of diagnosis enables risk factors to be identified in an early stage of RA. However, some possible limitations of the study should be recognized. Prospective research is inherently threatened by aspects of internal validity, and other unmeasured biomedical or psychosocial factors may account for the relationship to longterm distress. In addition, the generalizability of our findings might be limited due to some selection bias. All patients took part in a longterm clinical trial. Dropouts were also more distressed and scored higher on neuroticism than patients who completed all assessment points, possibly limiting the generalizability of our findings to patients with RA who are only moderately

distressed. However, this finding may also be interpreted as further evidence of the role neuroticism plays in psychological distress and may even have led to an underestimation of its effect on longterm distress.

Irrespective of these limitations, the relative strength of the effects found, particularly for the personality characteristic of neuroticism, underline the importance of paying close attention to factors other than RA when studying risk factors for heightening distress over time. In addition, screening for patients with lower education levels and higher levels of neuroticism may be highly recommended in clinical practice, since these patients are known to report physical symptoms that do not stem purely from RA disease activity. Consequently, they may benefit more from educational and multidisciplinary treatments than pharmacological treatment alone. While multidisciplinary treatments have been shown to be possibly effective in RA<sup>64,65</sup>, narrowly focusing on individual variability in these vulnerability factors may considerably improve their effects on longterm physical and psychological outcomes.

#### ACKNOWLEDGMENT

We thank G.A. van Albada-Kuiper, A.H. Bakker, I. van Booma-Frankfort, E.J. ter Borg, R. Brons, A.A. van Everdingen, H.C.M. Haanen, A.H.M. Heurkens, D.M. Hofman, R. Huisman, C.H.M. van Jaarsveld, A.W.J.M. Jacobs-van Bree, A.A. Kruize, H. van Mourik, I. Nuver-Zwart, Y. Schenk, D.R. Siewertsz-van Reesema, M.J. van der Veen, and S. van Wijk for data collection.

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