Comorbid Depression Is an Independent Risk Factor for Mortality in Patients with Rheumatoid Arthritis

DENNIS C. ANG, HYON CHOI, KURT KROENKE, and FREDERICK WOLFE

ABSTRACT. ***Objective.*** Whether comorbid depression increases mortality in patients with rheumatoid arthritis (RA) is unknown. Our objective was to determine whether the presence of depression predicted mortality in patients with RA.

Methods. We followed 1290 consecutive outpatients with RA who met our stringent inclusion criteria during an 18-year observation period. Since 1981, demographic, clinic, and self-report data were collected and entered into a computer database at the time of each clinic visit. The comorbidity data were consistently recorded beginning in 1991. Our primary independent variable was the mean of the Arthritis Impact Measurement Scales (AIMS) depression scores during the first 4 years of entry into the clinic cohort (average 4-year depression). Data were analyzed using Cox proportional hazard models.

Results. After adjusting for covariates, the hazard ratio (HR) for each unit increase in the average 4-year depression score on mortality was 1.14 ($p < 0.0001$). Using only the data obtained from 1991 to 2003, the mortality risk was slightly increased (HR 1.35, $p < 0.0001$). To reduce residual confounding due to RA disease activity and/or comorbid medical conditions, we then excluded deaths during the first 2 years after study onset. With this method, the HR for the average 4-year depression remained significant (HR 1.35, $p < 0.0001$). Because an AIMS depression score ≥ 4 is consistent with clinical depression, we analyzed the dataset using the average 4-year depression score as a dichotomous variable (score < 4 or ≥ 4). The HR of clinical depression on mortality was 2.2 (95% CI 1.2–3.9, $p = 0.01$).

Conclusion. Depression increases the risk of mortality in RA. Our study highlights the importance of comorbid depression in patients with RA. (J Rheumatol 2005;32:1013–9)

Key Indexing Terms:
DEPRESSION RHEUMATOID ARTHRITIS MORTALITY RISK FACTOR

Medical conditions are associated with an increased risk of depressive symptoms and disorders, particularly when the illness is chronic. Based on several studies that addressed the relative influence of different chronic diseases on patients' mental well being, cardiovascular conditions, stroke/neurologic disorders, renal disease, and musculoskeletal conditions are the chronic illnesses most frequently associated with psychological distress[1-5]. Functional incapacitation may partly explain these relationships[6].

Rheumatoid arthritis (RA) is a chronic medical disorder that causes pain, loss of function, systemic complications, and premature mortality. Depression has also been identified as a problem for persons with RA. Attempts to estimate the prevalence of depression in people with RA are complicated by conceptual and definitional problems. Most of the currently available self-administered depressive symptom scales assess the overall severity of depressive symptoms, and are not intended to be used as diagnostic instruments for case identification. In addition, certain somatic items on psychological questionnaires can be explained by coexisting medical disease (i.e., criterion contamination) rather than by psychological status, which may inflate estimates of the prevalence and severity of depressive symptoms. However, even when careful methods of assessment are applied, the prevalence of depression among patients with RA is conservatively estimated to be 15%–20%[7-9]. Indeed, patients with RA are twice as likely to suffer from depression as members of the general population.

Depression increases the burden of RA to the patient and society. Psychological distress, as measured by self-report depression scales, is associated with increased levels of

From the Division of Rheumatology, Indiana University School of Medicine, Indianapolis, Indiana; Arthritis Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Regenstrief Institute, Inc., and Division of General Internal Medicine and Geriatrics, Indiana University School of Medicine; and the National Data Bank for Rheumatic Diseases and University of Kansas School of Medicine, Wichita, Kansas, USA.

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D.C. Ang, MD, Division of Rheumatology, Indiana University School of Medicine; H. Choi, MD, MPH, DrPH, Arthritis Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School; K. Kroenke, MD, Regenstrief Institute, Inc. and Division of General Internal Medicine and Geriatrics, Indiana University School of Medicine; F. Wolfe, MD, National Data Bank for Rheumatic Diseases and University of Kansas School of Medicine, Wichita, Kansas, USA.

Address correspondence to Dr. F. Wolfe, National Data Bank for Rheumatic Diseases, 1035 North Emporia, Suite 230, Wichita, KS 67214. E-mail: fwolfe@arthritis-research.org

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pain[10,11]. However, the causal relationship between pain and depression may act in both directions, with pain increasing depression and depression increasing pain[12]. Further, depression is associated with increased functional disability in RA patients. Longitudinal studies have shown that the causal association between depression and self-reported disability may also be bidirectional[13-16]. Finally, depression has been linked to negative health outcomes and higher health costs for persons with RA[17,18]. Indeed, appropriate identification and subsequent treatment of depression are needed to maximize the quality of life for persons with RA.

Studies over the past decade suggest an association between depression and nonsuicide mortality. In a recent metaanalysis, Schultz, *et al*[19] found that the relative risk for depression as a predictor of mortality ranges from 1.2 to 4.0. The relationship of depression with mortality has been seen in various diseases including myocardial infarction [hazard ratio (HR) 2.4], stroke (risk ratio 1.1 to 2.4), mild dementia (odds ratio 4.3), endstage renal disease (relative risk 1.2), and diabetes mellitus (HR 2.6)[20-27]. Relatively little is known about the complex temporal relations among behavior, affect, and pathophysiology to account for the association between depression and mortality.

Although depression increases the personal and societal burden of RA, it is not known whether depression in patients with RA confers a higher mortality risk. Because depression is often a treatable illness, understanding the prognostic significance of depression in relation to mortality is important from a public health standpoint and for clinical management of RA. Our study had 3 objectives: (1) to examine whether comorbid depression in a clinic cohort of patients with RA predicts mortality; (2) to assess whether the depression-mortality relationship persists after controlling for comorbid medical illnesses and RA disease activity; and (3) to determine if the observed association between depression and mortality persists beyond the early years of study observation, insofar as deaths during the early years of study observation may be the result of the associated medical disorder (e.g., myocardial infarction) and not of secondary depression. We hypothesized that the effect of depression on mortality, independent of comorbid medical disorders, would persist beyond the early years of study observation.

MATERIALS AND METHODS

Patients. Since 1974, we have enrolled more than 2000 consecutive individuals with RA seen at the Wichita Arthritis Center, an outpatient rheumatology clinic. Demographic, lifetime comorbidity index, and clinic data [i.e., erythrocyte sedimentation rate (ESR) and grip strength] and self-report data were recorded and entered into a computer database at the time of each followup clinic visit. Self-report data included Health Assessment Questionnaire (HAQ) disability index score[28,29], visual analog scale (VAS) for pain, VAS for global severity of RA, and Arthritis Impact Measurement Scale (AIMS) for depression[30,31]. Systematic longitudinal lifetime comorbidity data collection was started in 1991. The lifetime comorbidity score is the sum of present or past comorbid condition reported by the patient. Conditions include cancer, stroke, fracture, and renal, endocrine, gastrointestinal, cardiovascular and hepatobiliary problems. Psychiatric diagnoses were not part of the comorbidity index. The lifetime comorbidity index has been shown to predict subsequent mortality[32].

Data analysis was restricted to patients fulfilling the 1958-87 American College of Rheumatology (formerly the American Rheumatism Association) criteria for RA[33,34] who attended the Wichita Arthritis Center at least twice between January 1, 1981 (when HAQ and AIMS depression scores first became available) and December 31, 2003. We ended followup when individuals died or on December 31, 2003. Our inclusion criteria resulted in a study population of 1290 patients and 102,942 patient-months of observation. Within the period of observation, there were 339 deaths.

Primary independent variable. The AIMS is a widely used rheumatic disease health status instrument for which reliability and validity have been well documented[35-39]. The AIMS depression scale has a score range from 0 (no depression) to 10 (worst depression). To ensure that we were capturing chronic depressive states rather than transient episodes, a single value of depression representing the mean of the first 4 years of entry into the cohort was used (average 4-year depression). The mean number of AIMS depression questionnaires completed was 9.3 ± 6.1. Because we were interested in the effect of the severity of depressive symptoms and depressive disorder on mortality, the average 4-year depression score was treated as both a continuous and a dichotomous variable. Depressive disorder was defined as a cutoff score of 4 or greater[9].

Definition of study onset and observation period. In this report, we defined study onset or Year '0' to be the beginning of the fifth year from the time the patient entered the cohort. As shown in Figure 1, if a patient entered the clinic cohort in January 1981, Year '0' would fall on January 1985. In other words, Year '0' always postdates study entry by 4 years. In the example provided in Figure 1, the observation period would be from Year '0' to Year 18, the year the patient died or was censored.

To determine whether average 4-year depression affects late mortality, we divided the observation period into different time periods (i.e., Year 0–2, Year 2–6, Year 6–11, Year 11–16, and Year > 16).

Primary dependent variable. The primary outcome measure was all-cause mortality. Death was confirmed by review of medical records, death certificates, and the National Death Index (National Center for Health Statistics, US Department of Health and Human Services, Hyattsville, Maryland). We obtained all available hospital records and all official death certificates from states in which there were decedents from our cohort, and coded specific cause of death according to the *International Classification of Diseases*, ninth revision. The details of this data set with respect to mortality have been reported[40].

Data analysis. We compared RA patients with and without depression at Year '0' using t tests for differences in means and chi-square for differences in proportions. The relationship between average 4-year depression and mortality was studied with Cox proportional hazard models. We used the following covariates in all analyses: age, sex, marital status, race, education, lifetime comorbidity index, disease duration at study entry, HAQ disability score, VAS global severity, VAS pain, ESR, grip strength, and calendar year. Calendar year at entry was controlled in the analyses because of the potential effect of any unmeasured confounder that might influence mortality (e.g., introduction of methotrexate in the mid-1980s). We used the Kaplan-Meier method to estimate survival differences between the depressed and nondepressed RA groups. We tested differences in the survival functions between groups using the log-rank method and Wilcoxon test. Since early-onset mortality may be related to variables other than depression, we were particularly interested in the log-rank test, which emphasizes failures in the tail of the survival curve.

Most deaths in RA are due to comorbid medical conditions. Deaths that occurred close to study onset may have been due to comorbid medical conditions rather than depression. To avoid overestimating the mortality risk attributable to average 4-year depression, we performed 3 different analyses: 1. Using the data obtained from 1981 to 2003, the first analysis excluded deaths during the first 6 years after study onset. Because we do not have

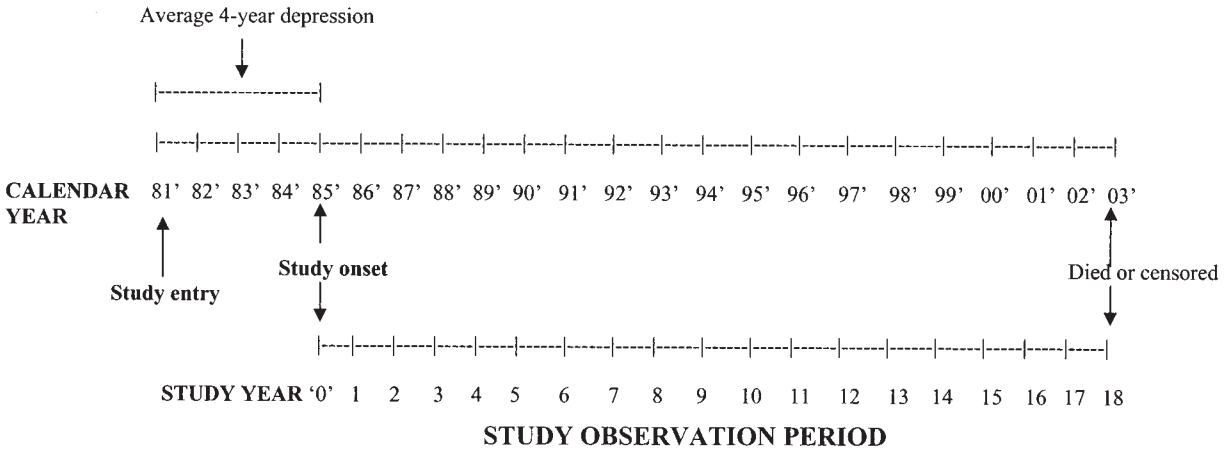

Figure 1. The study observation period. If a patient entered the cohort in January 1981, study onset or Year '0' would be January 1985. The patient's average 4-year depression score was the mean of the AIMS depression scores from January 1981 to December 1984.

good comorbidity data from 1985 to 1990, we made an assumption that death during the first 6 years after study onset may be caused by factors other than depression.

2. Because systematic collection of comorbidity data did not begin until 1991, the second analysis was conducted using only the data obtained from 1991 to 2003. In this second analysis, we counted all deaths from study onset until the time the patient was censored or died.

3. Using the 1991–2003 data, the third analysis excluded deaths during the first 2 years after study onset. We assumed that death during the early phase of the observation period might be related to RA disease activity or residual confounding from comorbid medical conditions.

Last, using the 1981–2003 data, we performed a stratified analysis to assess the independent effect of average 4-year depression on mortality at 4 different time periods (i.e., Year 0–2, Year 2–6, Year 6–11, Year 11–16, and Year > 16).

Variables for which missing data exceeded 5% were VAS global severity (5.7%), VAS pain (17.2%), and ESR (10.1%). For comorbidity data after January 1, 1991, there were 14.9% missing data points. Pain was missing because of a change in pain scales during this period. To determine if missing values for these variables were predictive of outcome, we ran an analysis that modeled for missing values. Specifically, missing data were modeled as follows, for example:

Y*i* = pain score for the *i*th patient if available; 0: if pain score was missing

Z*i* = 1: if pain score was missing for the *i*th patient; 0: otherwise

Our analysis revealed that patients with missing values for comorbidity (HR 1.3, p = 0.38), VAS global severity (HR 1.1, p = 0.91), VAS pain (HR 1.3, p = 0.81), or ESR (HR 2.6, p = 0.10) were not more likely to die than those for whom the data were complete. We then imputed missing values for ESR, VAS global severity, and VAS pain using the last observation carried forward method. Missing comorbidity data prior to 1991 were imputed using the first available comorbidity data. For patients seen only prior to 1991, comorbidity values were imputed using the mean comorbidity values for the cohort by sex.

We evaluated the proportional hazards assumption of the Cox model using a goodness-of-fit testing procedure. The significance level of all analyses was set at 0.05, and all tests were 2-tailed. Statistical computations were performed using Stata, version 8.0.

RESULTS

Patient characteristics at entry into the clinic cohort. The baseline demographic and clinical variables for the 1290 RA patients are presented in Table 1. At study entry, the mean disease duration was 6.6 years (median 3 yrs).

Comparison of depressed and nondepressed RA groups at Year 0. Using the average 4-year depression score ≥ 4 as representative of clinical depression, the study population yielded 228 depressed RA patients and 1062 nondepressed RA patients (prevalence rate = 17.6%). As shown in Table 2, there was no difference in terms of age, sex distribution, and disease duration at Year '0' between the 2 groups. However, compared to the nondepressed group, the depressed RA group was significantly more likely to be non-Caucasian, and less likely to be married and to have completed high school. Further, the depressed RA group had more associated comorbid illnesses and had worse measures of RA disease activity, such as HAQ disability score, VAS global severity, VAS pain, ESR, and grip strength.

Multivariable models of mortality. The unadjusted mortality HR for a 1-unit increase (worsening) in the average 4-year depression score (range 0–10) was 1.14 (95% CI 1.1–1.2, p < 0.0001). After controlling for demographics, calendar year, comorbidity, ESR, grip strength, and self-report data, the HR remained significant at 1.14 (95% CI 1.1–1.2, p <

Table 1. Demographic and clinical variables in 1290 patients with RA at time of entry into the clinic cohort. Except where indicated otherwise, values are the mean ± SD.

Age, yrs	55.3 ± 14.8
Sex, % female	72.4
High school graduates, %	81.0
Married, %	74.8
Caucasian, %	93.7
Disease duration, yrs	6.6 ± 8.6
Lifetime comorbidities, 0–11†	2.5 ± 1.9
Health Assessment Questionnaire disability score, 0–3	1.3 ± 0.3
Global severity, 0–10	5.3 ± 2.5
Pain, 0–10	5.1 ± 2.7
Erythrocyte sedimentation rate, mm/h	30 ± 24
Grip strength, mm Hg	122 ± 24
Average 4-year depression, 0–10	2.4 ± 1.4

† Last or maximum value.

0.0001). Using the 1991–2003 data, the adjusted HR increased to 1.35 (95% CI 1.1–1.6, p < 0.0001). When we excluded deaths during the first 2 years after study onset, the adjusted HR for the 1991–2003 data was unchanged at 1.35 (95% CI 1.1–1.6, p < 0.0001; Table 3). We also ran separate analyses without imputing data for missing values, and the findings were similar (data not shown).

As shown in Table 4, the stratified analysis revealed that the adjusted hazard ratios of the average 4-year depression on mortality at different time periods (i.e., Year 2–6, Year 6–11, and Year 11–16) were all significant.

After a median followup of 4.9 years, the clinically depressed RA group (i.e., patients with average 4-year depression score ≥ 4) was 2.2 times more likely to die than the nondepressed RA group (adjusted HR = 2.2, 95% CI 1.2–3.9, p = 0.01).

Kaplan-Meier estimates of survival in the depressed and nondepressed RA patient groups are presented in Figure 2. Both the log-rank and Wilcoxon tests showed statistically significant difference in the survival curves between the 2 groups, with the depressed RA group having a lower probability of survival.

Based on goodness-of-fit testing, our models satisfy the proportional hazards assumption (data not shown).

DISCUSSION

The data from this large prospective study of 1290 RA patients demonstrate that comorbid clinical depression is an independent predictor of all-cause mortality. RA patients with persistent or recurrent depression during the first 4 years of entry into the cohort were at least twice as likely to die than patients with no depression. After a median 5-year followup period, clinical depression, as defined by an AIMS depression score ≥ 4, was associated with higher mortality risk, independent of comorbid medical disorders and RA disease activity. Moreover, the effect of depression persists beyond the early years of the observation period, which suggests a true depression-mortality association rather than

Table 2. Comparison of depressed and nondepressed patients with RA at study onset or year '0'. Study onset or Year '0' was defined as the beginning of the 5th year from the time the patient entered the clinic cohort. Except where indicated otherwise, values are the mean ± SD.

	Depressed, N = 228	Nondepressed, N = 1062	p
Age, yrs	57.1 ± 14.1	57.2 ± 13.9	0.80
Sex, % female	73.3	73.6	0.56
High school graduates, %	72.8	86.3	< 0.001
Married, %	77.9	79.9	0.003
Caucasian, %	91.1	94.4	0.0001
Disease duration, yrs	7.2 ± 0.6	6.5 ± 0.3	0.11
Lifetime comorbidities, 0–11	2.7 ± 1.9	1.9 ± 1.6	< 0.0001
HAQ disability score, 0–3	1.7 ± 0.7	1.1 ± 0.7	< 0.0001
Global severity, 0–10	6.1 ± 2.2	3.9 ± 2.4	< 0.0001
Pain, 0–10	5.9 ± 2.4	4.0 ± 2.6	< 0.0001
Erythrocyte sedimentation rate	34.8 ± 0.4	29.3 ± 0.2	< 0.0001
Grip strength	104.4 ± 0.8	124.4 ± 0.4	< 0.0001

Table 3. Multivariate models of the relation of depression with mortality in patients with RA.

	Adjusted* Hazard Ratio	95% CI	p
Analysis 1			
Data from 1981 to 2003, excluded deaths during the first 6 years after study onset			
Average 4-year depression†	1.14	1.1–1.2	< 0.0001
Analysis 2			
Data from 1991 to 2003			
Average 4-year depression†	1.35	1.1–1.6	< 0.0001
Analysis 3			
Data from 1991 to 2003, excluded deaths during the first 2 years after study onset			
Average 4-year depression†	1.35	1.1–1.6	< 0.0001

* Adjusted for the following covariates: age, education, race, sex, marital status, lifetime comorbidities, disease duration and calendar year at study entry, Health Assessment Questionnaire disability score, VAS global severity, VAS pain, ESR, and grip strength. † Average 4-year depression score range from 0 (no depression) to 10 (worst depression). The hazard ratios reflect the risk of dying per one-unit increase in the average 4-year depression score.

Table 4. Stratified analysis of the effect of average 4-year depression on mortality at different time periods during the observation period.

	Adjusted HR*	95% CI	p
Average 4-year depression			
Year 2–6	2.9†	2.5–3.3	< 0.0001
Year 6–11	1.8†	1.7–1.9	< 0.0001
Year 11-16	1.4†	1.3–1.5	< 0.0001

* Adjusted for the following covariates: age, education, race, sex, marital status, lifetime comorbidities, disease duration and calendar year at study entry, Health Assessment Questionnaire (HAQ), VAS global severity, VAS pain, ESR, and grip strength. † In reference to Year 0–2, the adjusted hazard ratios were the mortality risk of the average 4-year depression at each time period.

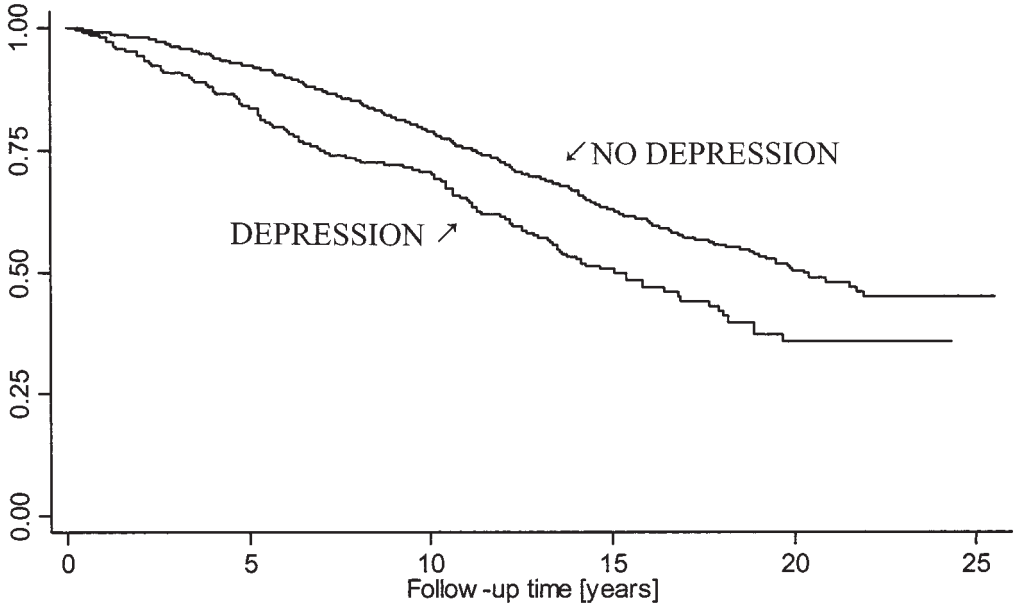

Figure 2. Survival rates over 20-year followup of RA patients with and without comorbid depression (log-rank test: chi-square = 19.37, p < 0.00001; Wilcoxon test: chi-square = 23.13, p < 0.00001).

confounding from the presence of other chronic illnesses. Consistent with previous reports[7-9], our study also confirms a substantial 17.6% prevalence of clinical depression in RA.

Our study has several limitations. Serious comorbid medical conditions can increase mortality directly and/or indirectly, through the mediating influence of depression. Some experts would argue that the observed relationship between depression and mortality in this RA cohort may be confounded by comorbid medical disorders. To address this problem, we did sensitivity analyses and excluded deaths within the first 2 years of study onset, and even extended the exclusion period up to 6 years to reduce residual confounding. In addition, if the data were biased toward early deaths caused by comorbid illnesses, we would expect the survival curves to come together during the later part of the observation period. As seen in Figure 2, this was not the case. The log-rank test, which places emphasis on the latter part of the survival curves, showed a statistically significant difference between the depressed and nondepressed RA groups. Similarly, when we divided the observation period into 4 different time periods, the depression-mortality relationship persisted well beyond the first 2 years after study entry. It is of particular importance that late mortality was increased in patients with depression.

Further, we do not have additional objective measures of RA disease activity (e.g., joint count) to control for in the analyses. As shown in a previous study[41], about 20% of the variance in depression change scores could be accounted for by changes in RA-related clinical variables. However, HAQ is a good surrogate marker of disease activity and provides information similar to many traditional measures in RA, such as the joint count, radiographic score, ESR, grip strength, button test, and walking time[42]. A recent report concluded that the usual laboratory, radiographic, and physical examination data relevant to RA patients were substantially weaker than the HAQ in predicting mortality[32,43]. With the combination of HAQ, ESR, and grip strength available in our dataset, we believe it unlikely that our findings were seriously confounded by the lack of additional indicators of RA disease activity. Third, that our dataset comes

from a single arthritis center may potentially limit its generalizability. However, the mortality rate among our participants was comparable to that of other RA cohorts, especially those in similar settings[44-46]. Similarly, the prevalence of depression in our sample is equivalent to what has been reported[7-9]. Fourth, the AIMS depression scale has not been validated for strict psychiatric case detection. In a previous study[9], however, an AIMS depression cutpoint of 4 was found to be comparable to a Center for Epidemiological Studies Depression Scale (CES-D) cutpoint of 23, a score that best discriminated between cases and noncases of depression among outpatients from mental health centers and community residents[47]. Finally, because our depression was based on a mean of the scores during the first 4 years of entry into the cohort, we cannot comment about the effect of depression on mortality during those earlier years. Incidentally, our analysis yielded similar results when an average 2-year (rather than 4-year) depression score was modeled with all the covariates (data not shown).

By what mechanism does a process of the mind affect the outcome of processes of the body? While the exact mechanisms underlying the association are not known, possible biobehavioral mechanisms include (1) autonomic dysregulation[48]; (2) inflammation[49]; (3) impaired cellular immunity[50,51]; (4) treatment nonadherence[52]; and (5) insulin resistance[53]. Increased platelet aggregation may also be a contributory factor[54,55].

Our study highlights the importance of a person's psychological state, specifically depression, as an important independent predictor of mortality in patients with RA. In a previous report, Pincus, *et al* noted "helplessness score" to be associated with mortality[56]. Despite some overlapping features between "helplessness" and depression, the 2 constructs are not identical. One of the strengths of our study was the availability of mean depression scores over a 4-year period, which ensured that we were dealing with chronically depressed RA patients, and not transient bouts of depressive symptoms.

Our findings have important implications for clinical care. Depression is frequently unrecognized and undertreated in medical patients, a problem most extensively studied in primary care, but apparently also the case for a variety of medical specialty settings including rheumatology[57-64]. Because of the enormous personal and societal impact of RA, healthcare providers should be alert to the diagnosis of depression. Adequate treatment of depression can improve both physical and psychological health status of patients with RA[65]. Although one can postulate that treating depression might reduce mortality risk, clinical trials would be necessary to test this hypothesis.

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