

Relationship Between Depression and Disease Activity in United States Veterans With Early Rheumatoid Arthritis Receiving Methotrexate

Alan M. Rathbun¹, Bryant R. England² , Ted R. Mikuls², Alice S. Ryan³, Jennifer L. Barton⁴, Michelle D. Shardell⁵, and Marc C. Hochberg⁶

ABSTRACT. *Objective.* Depression is common in patients with rheumatoid arthritis (RA), exacerbates disease activity, and may decrease response to first-line disease-modifying antirheumatic drugs. This study aimed to determine if depression affects disease activity among veterans with early RA prescribed methotrexate (MTX). *Methods.* Participants included veterans enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) registry with early RA (onset < 2 yrs) prescribed MTX. Depression was assessed at enrollment using the International Classification of Diseases, 9th revision codes (296.2–296.39, 300.4, 311). Disease activity was measured using the Disease Activity Score in 28 joints (DAS28) and other core measures of RA disease activity. Propensity score weights were used to adjust depressed (n = 48) and nondepressed (n = 220) patients on baseline confounders within imputed datasets. Weighted estimating equations were used to assess standardized mean differences in disease activity between depressed and nondepressed patients at 6-month, 1-year, and 2-year follow-ups. *Results.* The analytic sample was composed of 268 veterans with early RA prescribed MTX who were predominantly male (n = 239, 89.2%) and older (62.7 yrs, SD 10.6) than patients with RA in the general population. Adjusted estimates indicated that depression was associated with significantly higher DAS28 at 6 months (β 0.35, 95% CI 0.01–0.68) but not at the 1- or 2-year follow-up. Also, depression was associated with significantly worse pain at 6 months (β 0.39, 95% CI 0.04–0.73) and 1 year (β 0.40, 95% CI 0.04–0.75). *Conclusion.* In early RA, depression is associated with greater short-term disease activity during MTX treatment, as well as more persistent and severe pain.

Keywords Indexing Terms: depression, disease activity, disease-modifying antirheumatic drugs, rheumatoid arthritis

This study was supported by the Rheumatology Research Foundation's Scientist Development Award and grants from the National Institute on Aging (NIA; K01 AG064041, R01 AG048069, P30 AG028747), Veterans Affairs (VA) Clinical Science Research and Development Service (I01 BX004660), and National Institute of General Medical Sciences (U54 GM115458).

¹A.M. Rathbun, PhD, MPH, Department of Epidemiology and Public Health, and Department of Medicine, University of Maryland Baltimore, School of Medicine, Baltimore, Maryland; ²B.R. England, MD, PhD, T.R. Mikuls, MD, MSPH, VA Nebraska-Western Iowa Health Care System, and Department of Internal Medicine, University of Nebraska Medical Center, College of Medicine, Omaha, Nebraska; ³A.S. Ryan, PhD, Department of Medicine, University of Maryland Baltimore, School of Medicine, and VA Maryland Health Care System, Baltimore, Maryland; ⁴J.L. Barton, MD, MCR, VA Portland Health Care System, and Department of Medicine, Oregon Health & Science University, School of Medicine, Portland, Oregon; ⁵M.D. Shardell, PhD, Department of Epidemiology and Public Health, University of Maryland Baltimore, School of Medicine, Baltimore, Maryland; ⁶M.C. Hochberg, MD, MPH, Department of Epidemiology and Public Health, and Department of Medicine, University of Maryland Baltimore, School of Medicine, and VA Maryland Health Care System, Baltimore, Maryland, USA.

AMR is supported by grants from the Rheumatology Research Foundation and National Institute on Aging (NIA; K01 AG064041). BRE and TRM are supported by grants from the Rheumatology Research Foundation, VA Clinical Science Research and Development Service (I01 BX004660), and National Institute of General Medical Sciences (U54 GM115458). JLB is supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (K23 AR064372). ASR is supported by grants from the VA Rehabilitation Research and Development Service (N9273, I01 RX002790, I01 RX001461, I21 RX002870), NIA (P30 AG028747), and National Institute on Diabetes and Digestive and Kidney Disease (P30 DK072488). MDS is supported by grants from NIA (R01 AG048069). MCH is the President of Rheumcon Corporation and receives consulting fees from Bioiberica SA, Bristol Myers Squibb, Eli Lilly, EMD Serono, Galapagos, IBSA Biotechniq SA, Novartis Pharma AG, Pfizer, Plexxikon, Samumed LLC, Theralogix LLC, and TissueGene Inc. Address correspondence to Dr. A.M. Rathbun, Howard Hall Suite 200, 660 W. Redwood Street, University of Maryland School of Medicine, Baltimore, MD 21201, USA. Email: arathbun@som.umaryland.edu. Accepted for publication November 3, 2020.

Rheumatoid arthritis (RA) is an autoimmune, inflammatory joint disorder, which affects 1.3 million American adults, and causes joint pain and permanent physical disability.^{1,2} RA disease burden extends beyond the joints, and extraarticular manifestations include poor psychosocial health, especially depression.^{3,4} Major depression affects approximately 17% of RA patients, and more than one-fifth report a history of depressive symptoms.^{5,6} Depression exacerbates the societal and economic costs of RA and is associated with an increased risk of work disability, higher medical care costs, and greater comorbidity and mortality.^{7,8,9} These detrimental effects are related to the underrecognition and undertreatment of depression among patients with RA, contrasting with clinical guidelines recommending that physicians be cognizant of depression in those with chronic physical diseases.¹⁰

The unique occupational demands of military service have resulted in an increasing awareness concerning the burden of concurrent musculoskeletal and psychiatric disorders (e.g., RA and depression) among United States veterans.¹¹ Evidence also suggests the relationship between musculoskeletal and psychiatric disorders among veterans is bidirectional.¹¹ Prior research supports this contention and indicates that depression onset in RA is preceded by worsening severity in patient- and physician-reported RA disease activity measures.^{12,13} Similarly, depressive symptoms are associated with slower declines in RA disease activity as measured by patient- and physician-reported metrics.¹³ Analogous results regarding the association of depression with RA disease activity have been found among US veterans.¹¹ Given that depression worsens the severity and progression of RA disease activity, it may adversely affect clinical response to standard therapies.³

The current treat-to-target paradigm involves identifying a target (e.g., remission) during therapy, routinely evaluating disease activity, and regularly adapting treatment if the target is not achieved.¹⁴ Medical comorbidities may influence RA disease activity and progression, and, in turn, response to pharmacologic therapy; thus, it is critical to understand how depression affects RA treatment outcomes.^{3,4} Several studies have shown that depression is associated with worse clinical response to biologic disease-modifying antirheumatic drugs (bDMARDs).^{3,15,16,17} However, bDMARDs are used after patients with RA have not responded to conventional synthetic DMARDs (csDMARDs).¹⁸ Methotrexate (MTX) is the preferred csDMARD for RA treatment because of its superior efficacy and tolerability profile, accounting for 60% of first-line medication prescriptions in veterans with RA.¹⁹ Nonetheless, approximately 40% of patients with RA do not have a clinical response to MTX, and poor psychosocial health is associated with nonresponse.²⁰

Research assessing the efficacy of RA treatments in the presence of depression is necessary, particularly MTX, which has not been rigorously evaluated in the context of psychiatric comorbidity.³ Given the high rate of depression among US veterans with RA and their underutilization of MTX despite being the optimal first-line therapy, the current study aimed to determine whether this comorbidity affects disease activity in patients with early RA treated with MTX.^{11,18,21} It was hypothesized that

veterans with concurrent RA and depression experience worse disease activity than those without depression, despite MTX treatment.

METHODS

Study data and sample. The current study used data from the Veterans Affairs Rheumatoid Arthritis (VARA) registry, a cohort study of US veterans with RA, and design details are available elsewhere.²² Briefly, VARA is a multi-center study that enrolled US veterans satisfying the revised 1987 American College of Rheumatology (ACR) RA classification criteria.²³ Participants were from 1 of 13 VA medical centers, and medications and ACR core measures of RA disease activity were recorded at each clinical encounter.²² All patients provided written informed consent before enrollment into the VARA study, which was approved by an institutional review board (IRB) at each participating VA medical center. The current research was approved by the VARA Scientific and Ethics Advisory Committee and University of Maryland Baltimore IRB (HP-00075981). Patients with RA (n = 2692) who enrolled in the VARA registry from October 2002 to October 2018 were included in the current study (Figure 1). For this study, the VARA cohort was restricted to 635 individuals with new disease onset (duration < 2 yrs) at the time of enrollment, in order to include those veterans with RA who were most likely to have had a recent diagnosis and initiated their first csDMARD. Medication utilization, including glucocorticoids, bDMARDs, and csDMARDs, was recorded during clinical encounters, and the analytic sample of veterans with early RA was further limited to those participants receiving MTX (n = 268).^{11,24} The analytic sample represented 1662 clinical encounters among 268 veterans with early RA treated with MTX.

Depression. The lifetime prevalence of depression has been demonstrated to influence the evolution of RA disease activity among veteran and general-population RA patients.^{11,25} Additionally, the small number of veterans with early RA being treated with MTX precluded (i.e., insufficient statistical power) a study design that excluded prevalent depression cases and identified incident depressive episodes prospectively. Thus, the primary exposure was operationalized as prevalent depression, occurring before or after RA onset, which was assessed upon enrollment into the VARA registry. More specifically, treating providers enter comorbid conditions into the VARA database during enrollment using an associated International Classification of Disease, 9th revision (ICD-9) code.¹¹ In contrast with other VA studies using administrative diagnostic codes for case ascertainment, comorbid conditions were not measured based on outpatient or inpatient claims data reported within specified time periods.²⁶ Prevalent depression at study baseline measured and entered in to the VARA registry database by enrolling providers was defined using ICD-9 codes 296.2-296.39, 300.4, and 311.

Disease activity. Differences in treatment-associated clinical outcomes were assessed using composite disease activity and ACR core measures of RA disease activity.^{27,28} The primary outcome was the Disease Activity Score in 28 joints (DAS28), a measure incorporating tender (TJC) and swollen joint counts (SJC) based on 28 counts, patient global assessment of disease activity (PtGA; visual analog scale [VAS] 0–100 mm), and erythrocyte sedimentation rate (ESR; mm/h), which is calculated using a mathematical formula: $DAS28 = 0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.70 \times \ln(ESR) + 0.014 \times PtGA$.²⁸ Consistent with pharmacoepidemiologic recommendations, secondary outcomes included the disaggregated DAS28 components as well as the provider global assessment of disease activity (PRGA; VAS 0–100 mm), patient-reported pain (VAS 0–10 cm), and functional disability assessed using the Multidimensional Health Assessment Questionnaire (MDHAQ).^{29,30} Outcome measures were standardized (i.e., [observation-pooled sample mean]/pooled sample SD), such that distributions were mean centered and normalized (i.e., mean = 0, SD = 1) and effect estimates could be interpreted in terms of SDs. Differences of 0.15, 0.4, and 0.75 SDs correspond to small, medium, and large effect sizes among older samples, respectively.³¹ To address skewness of data, the SJC, TJC,

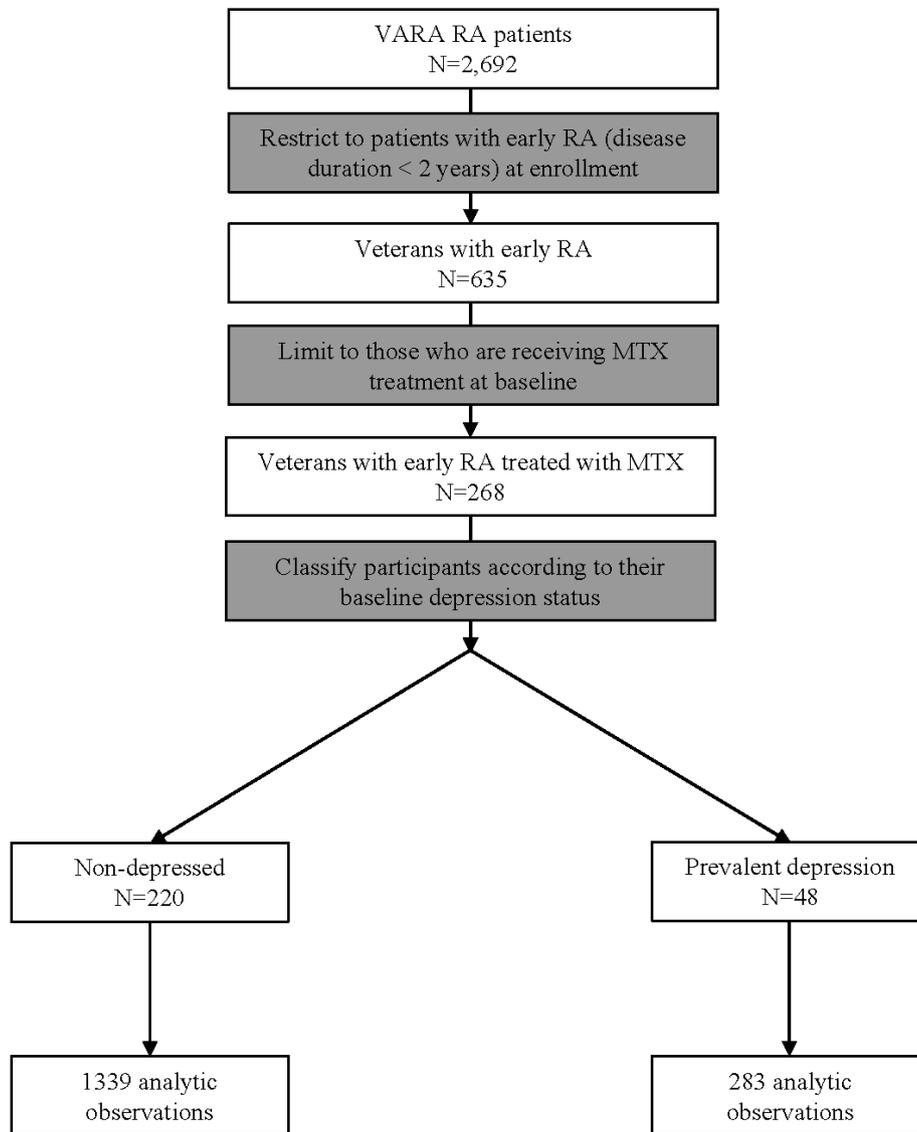


Figure 1. Study sample flow diagram. MTX: methotrexate; RA: rheumatoid arthritis; VARA: Veterans Affairs Rheumatoid Arthritis registry.

and ESR distributions were log-transformed before standardization, and if applicable, shifted by the lowest nonzero value. Due to between-person variability in the timing of data collection dictated by routine clinical care, RA disease activity was assessed from baseline through 2 years of follow-up as a trajectory, and 6-month and 1- and 2-year between-group differences in outcome measures were estimated to evaluate how depression affects disease activity during MTX treatment.

Potential confounders. Participant characteristics selected *a priori* as potential confounders were identified from prior studies of depression in patients with RA.^{13,16,25} Demographic and behavioral variables included age (yrs), sex (male or female), race (White or non-White), smoking status (current, former, never), and BMI (kg/m²). Comorbidity was assessed using a modified version of the rheumatic disease comorbidity index (RDCI), a composite scale (range 0–8) comprising 11 different medical conditions.³² In the current study, the RDCI omitted depression and was calculated using the following formula: $2 \times \text{lung disease} + (2 \times [\text{heart attack, other cardiovascular disease, or stroke}] + 1 \times \text{hypertension}) + \text{fracture} + \text{diabetes} + \text{cancer} + (\text{ulcer or stomach problem})$. Concomitant treatments included hydroxychloroquine, sulfasalazine, leflunomide, and tumor necrosis factor

inhibitors (TNFis); notably, no participants included in the current study were receiving non-TNFi bDMARDs at baseline. Disease activity exhibits intraindividual clustering, and baseline values are the strongest predictor of RA treatment response.³³ Without accounting for differences in baseline disease activity between depressed and nondepressed participants, any association between depression and treatment response could be due to residual confounding.¹⁶ Baseline disease activity measures (SJC, TJC, PtGA, PRGA, ESR, MDHAQ, pain) were included as covariates to remove them as a potential source of confounding.³³

Statistical analysis. Baseline characteristics in the original study sample were assessed using means and SDs or medians and IQRs for continuous variables, and frequencies and percentages for categorical measures. *T* tests or Wilcoxon rank-sum tests and chi-square tests were used to evaluate differences in baseline characteristics between depressed and nondepressed participants for continuous and categorical variables, respectively. Missing values for smoking, BMI, SJC, TJC, ESR, PtGA, PRGA, pain, MDHAQ, and DAS28 were imputed from fully observed variables (age, sex, race, comorbidity, and concomitant treatments) using a multilevel, multiple imputation by chained equations.³⁴ Fraction of missing data for every estimation variable

across different outcome models was never > 10%, and estimates for the main effect of depression converged and changed little as new imputations were added after 20 datasets; thus, 20 datasets were imputed and analyzed.

Propensity score (PS) weights were used to control for between-group differences in baseline covariates to promote causal interpretations regarding the effect of depression on disease activity.³⁵ Inverse probability weights implemented in the PS context account for differences in the probability of exposure between 2 comparison groups by weighing the exposed and unexposed to represent the overall study sample. Boosted regression models were used to estimate PS weights, an approach that outperforms other estimation methods in terms of bias reduction.³⁶ The generalized boosted model is a machine-learning algorithm involving an iterative process of fitting multiple regression trees to evaluate and define complex and nonlinear relationships between exposure and covariates without overfitting data.³⁶ An exposure model was fit by regressing depression status on covariates using the boosting algorithm separately on 20 imputed datasets to estimate weights. Standard methods for evaluating PS weights were conducted to assess the validity of the underlying theoretical assumptions.³⁷

PS weighted generalized estimating equations (i.e., weighted estimating equations [WEE]) modeled outcome trajectories and estimated differences in RA disease activity between depressed and nondepressed participants.³⁸ Locally weighted scatterplot smoothing (LOWESS) is a nonparametric regression method that fits smoothing curves between predictors and outcomes while relaxing traditional modeling constraints.³⁹ LOWESS curves were used to conduct exploratory assessments of time trends and showed nonlinear longitudinal functional forms for every outcome measure. Therefore, WEE clustered by participants modeled outcome trajectories as a cubic function (i.e., time + time² + time³) to address nonlinearity and had a categorical indicator for depression, 3 continuous variables for time, and statistical interactions between depression and time variables. Models were estimated across multiple imputed datasets, and results were pooled using Rubin's combining rules.³⁴ Causal mean differences in clinical outcomes between depressed and nondepressed participants were interpolated at 6-month and 1- and 2-year follow-up. Tests were 2-sided, an α level of 0.05 was used, and all analyses were conducted with R statistical software (version 3.4.1; R Foundation for Statistical Computing).

RESULTS

Sample characteristics. The original study sample included 48 and 220 depressed and nondepressed veterans with early RA who were being prescribed MTX at baseline and had 283 and 1339 analytic observations, respectively. The prevalence of major depressive disorder in this sample was approximately 18%, and comorbid depression was associated with younger age and more comorbid conditions, but between-group differences in distributions for other covariates were not statistically significant (Table 1). Substantially more depressed than nondepressed patients with RA were using hydroxychloroquine (47.9% vs 31.8%), and disease activity measures (DAS28, TJC, SJC, PtGA, pain, MDHAQ) were consistently numerically higher in participants with depression compared with those without, although these associations did not reach statistical significance.

Composite disease activity. DAS28 trajectories (Figure 2) showed faster initial disease activity decline after study enrollment that plateaued by 6-month follow-up in veterans with early RA receiving MTX who did not have comorbid depression. By contrast, depressed participants experienced slower treatment-associated decreases in disease activity that did not intersect with nondepressed participants until after more than 1 year of follow-up. Depression in veterans with early RA treated with

MTX was associated with significantly worse disease activity at 6-month follow-up, where depressed participants had DAS28 scores approximately 0.35 SDs (95% CI 0.01–0.68, $P = 0.045$) higher than nondepressed participants (Table 2). However, the differences in DAS28 scores between those with and without depression decreased over time. The associations between baseline depression and DAS28 at 1-year (β 0.15, 95% CI –0.26 to 0.55, $P = 0.48$) and 2-year (β –0.07, 95% CI –0.60 to 0.46, $P = 0.80$) follow-up were smaller in magnitude and not statistically significant.

Core component measures. Analogous to DAS28 results, effect estimates for the SJC, TJC, PtGA, and ESR at 6-month follow-up ranged from 0.21 to 0.27 SDs, indicating higher disease activity among those with depression; however, the associations were not statistically significant (Table 2). The magnitude of the associations for DAS28 component measures also decreased over time, and between-group differences were negligible by 2-year follow-up. In contrast with the DAS28 and its component measures, depression was associated with significantly higher patient-reported pain: 0.39 SDs (95% CI 0.04–0.73, $P = 0.03$) at 6-month and 0.40 SDs (95% CI 0.04–0.75, $P = 0.03$) at 1-year follow-up. However, associations for the PRGA and MDHAQ were smaller in comparison, not statistically significant, and generally decreased in magnitude over time.

DISCUSSION

The current study examined disease activity trajectories among depressed and nondepressed veterans with early RA receiving MTX therapy, and findings indicate that depression among these patients is associated with higher disease activity during the initial stages of treatment and with more persistent pain after MTX initiation. More specifically, veterans with concurrent early RA and depression had significantly higher disease activity as measured by the DAS28 6 months after documented prescription of the most utilized first-line csDMARD. However, differences in disease activity between depressed and nondepressed participants decreased as time progressed, and DAS28 associations at 1- and 2-year follow-up were not statistically significant. By contrast, depression was associated with more persistent and severe self-reported pain as measured by VAS during the first year of follow-up among veterans with early RA who were enrolled in VARA and prescribed MTX. Collectively, results suggest that depression could cause slower initial declines in disease activity after MTX treatment initiation among patients with early RA, as well as worse pain that may be related to the primary condition or a consequence of other mechanisms associated with psychiatric comorbidity.

Findings are congruent with previous studies in civilian populations, demonstrating that depression among patients with RA receiving bDMARDs is associated with slower and/or reduced treatment response.^{3,15,17} Moreover, study results validate epidemiologic data from a national RA registry showing prevalent depression to predict slower Clinical Disease Activity Index (CDAI) declines and a reduced probability of CDAI clinical

Table 1. Baseline characteristics of depressed and nondepressed participants in the original analytic sample (n = 268).

	Depressed, n = 48		Nondepressed, n = 220		P
Age, yrs	58.86	(10.04)	63.48	(10.56)	0.006
Male, n (%)	41	(85.4)	198	(90.0)	0.50
White, n (%)	39	(81.2)	171	(77.7)	0.73
Smoking status, n (%)					0.48
Former	24	(50.0)	121	(56.3)	
Current	16	(33.3)	54	(25.1)	
Never	8	(16.7)	40	(18.6)	
BMI, kg/m ²	29.67	(5.10)	28.93	(5.33)	0.46
Comorbid conditions, n (%)	1.90	(1.31)	1.45	(1.38)	< 0.001
Hydroxychloroquine, n (%)	23	(47.9)	70	(31.8)	0.05
Sulfasalazine, n (%)	9	(18.8)	31	(14.1)	0.55
Leflunomide, n (%)	2	(4.2)	7	(3.2)	1.00
TNFi, n (%)	5	(10.4)	30	(13.6)	0.72
TJC (0–28)	5.50	(2.00–13.00)	4.00	(1.00–10.00)	0.18
SJC (0–28)	4.00	(2.00–10.00)	4.00	(1.00–8.75)	0.49
ESR, mm/h	20.00	(9.00–38.00)	24.00	(10.00–42.50)	0.35
PtGA (0–100 mm)	48.49	(26.11)	39.65	(27.55)	0.07
PRGA (0–100 mm)	34.37	(23.06)	34.66	(23.90)	0.95
Pain (0–10 cm)	5.16	(2.79)	4.30	(2.91)	0.10
MDHAQ (0–3)	0.96	(0.58)	0.81	(0.65)	0.23
DAS28	4.32	(1.58)	4.08	(1.65)	0.43

Values expressed as mean (SD) or median (IQR) unless indicated otherwise. DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; MDHAQ: Multidimensional Health Assessment Questionnaire; PRGA: provider global assessment; PtGA: patient global assessment; SJC: swollen joint count; TJC: tender joint count; TNFi: tumor necrosis factor inhibitors.

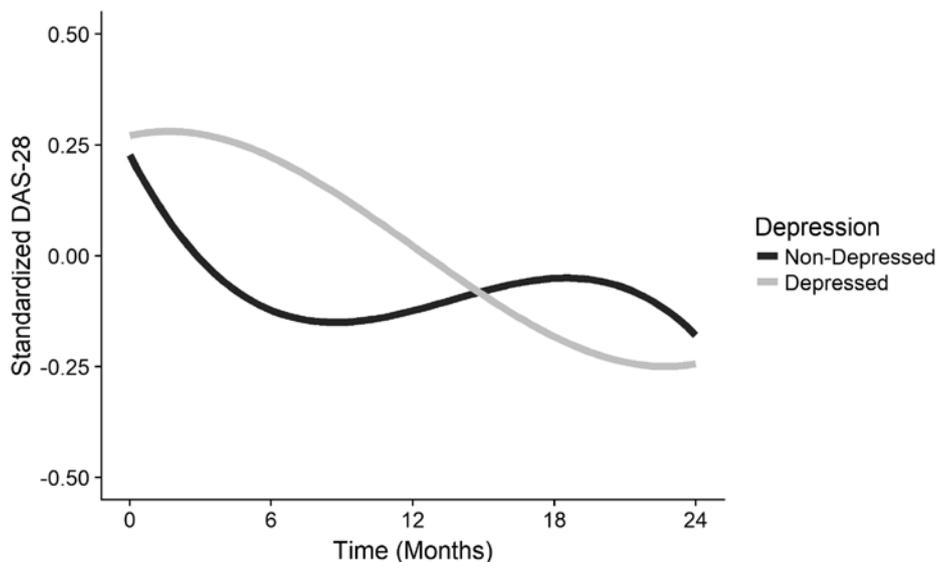


Figure 2. DAS28 trajectories in depressed and nondepressed veterans with early rheumatoid arthritis during treatment with methotrexate. DAS28: Disease Activity Score in 28 joints.

remission 6 months after initiating biologic therapy.^{16,25} Evidence suggests the detrimental effect of depression on RA treatment response as measured by composite indices is primarily related to its negative correlation with PtGA.^{16,30} However, findings from the present study diverge from prior research, as estimated associations for the DAS28 components at 6-month follow-up were

all similar in magnitude (0.21–0.27 SDs). Although statistically insignificant and with small effect sizes, depression's collective influence on its component measures corresponded with a potentially meaningful, small-to-medium effect size–based difference in DAS28 at 6-month follow-up.³¹ These broader and more uniform effects of depression on disease activity in

Table 2. Standardized mean differences in RA disease activity at 6 months and 1- and 2-year follow-up comparing those with prevalent depression to those without depression at baseline.

	β	6 Months 95% CI	<i>P</i>	β	1 Year 95% CI	<i>P</i>	β	2 Years 95% CI	<i>P</i>
DAS28	0.35	(0.01–0.68)	0.045	0.15	(–0.26 to 0.55)	0.48	–0.07	(–0.60 to 0.46)	0.80
SJC	0.24	(–0.03 to 0.52)	0.09	0.09	(–0.24 to 0.43)	0.59	0.06	(–0.57 to 0.68)	0.86
TJC	0.25	(–0.06 to 0.56)	0.12	0.12	(–0.25 to 0.48)	0.54	–0.06	(–0.67 to 0.55)	0.85
PtGA	0.27	(–0.06 to 0.59)	0.11	0.28	(–0.03 to 0.58)	0.08	–0.04	(–0.71 to 0.63)	0.90
ESR	0.21	(–0.16 to 0.57)	0.26	0.01	(–0.34 to 0.38)	0.94	–0.02	(–0.58 to 0.54)	0.95
PRGA	0.14	(–0.17 to 0.45)	0.38	0.19	(–0.16 to 0.53)	0.30	–0.23	(–0.95 to 0.49)	0.53
Pain	0.39	(0.04–0.73)	0.03	0.40	(0.04 to 0.75)	0.03	0.11	(–0.50 to 0.72)	0.74
MDHAQ	0.15	(–0.18 to 0.47)	0.37	0.09	(–0.28 to 0.47)	0.62	0.03	(–0.48 to 0.53)	0.92

DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; MDHAQ: Multidimensional Health Assessment Questionnaire; PRGA: provider global assessment; PtGA: patient global assessment; RA: rheumatoid arthritis; SJC: swollen joint count; TJC: tender joint count.

veterans compared with non-veteran patients with RA may be a consequence of their demographic and occupational characteristics. First, the VARA sample is predominantly male and older, and sex differences have been observed in the clinical manifestation and progression of both RA and depression.^{40,41} In addition, veterans are often subject to chronic exposure to highly stressful experiences during military service, which may activate biopsychosocial processes that underly and exacerbate chronic conditions, particularly musculoskeletal and psychiatric disorders.^{42,43} Nonetheless, this is the first study, to our knowledge, to replicate and build upon previous findings showing poor psychosocial health as a risk factor for primary nonresponse to MTX treatment in patients with RA.²⁰

Among the ACR core component disease activity measures, depression was associated with persistently higher, small-to-medium effect size–based differences in patient-reported pain, which is analogous to results in prior studies among veterans and other RA samples treated with bDMARDs.^{3,11,17} However, these findings may not represent higher RA disease activity (i.e., nociceptive pain), as differences in physician-reported tender joints were smaller and not statistically significant. Additionally, depressed participants' self-reported pain scores converged with nondepressed participants by 2-year follow-up. Chronic pain among depressed veterans with early RA receiving MTX may be related to their depressive symptomology, which could exacerbate cognitive perceptions related to reporting pain or increase non-nociceptive pain by affecting physical activity and neurotransmitters related to pain sensitization.³ Unlike prior studies, the current research yielded no detectable signals between depression and TJC or MDHAQ, and therefore, more persistent and severe pain ratings related to depressed moods could be a measurement response shift arising from the negative effect associated with depressive symptoms.^{3,17,25} Alternatively, male patients with RA experience slower disease progression, underreport pain, and overestimate function compared with women, and participants may have had less extant joint damage and nociceptive pain than more representative samples, implying depression's effect on RA disease activity could be larger in female patients treated with MTX.^{40,44,45} Nonetheless, convergence in self-reported

pain scores after 2 years suggests depressed patients received additional medical care beyond MTX treatment. For example, veterans with early RA and depression could have escalated their RA treatment with bDMARDs in the presence of persistent pain.¹⁴ High-intensity depressive symptoms leading to greater pain perception and sensitivity, despite MTX treatment, may also cause patients to seek alternative provider-management options (e.g., antidepressants, cognitive behavioral therapy) for chronic pain.⁴⁶ Whether due to measurement response tendencies or substantive effects on pain sensitization, persistently higher pain ratings while receiving first-line RA treatment among depressed veterans with early RA represent a gap in clinical care. Given depressed patients were also younger, findings emphasize the need for better interventions as veterans with RA will live longer.

There are several study limitations. First, identification of new MTX users with an exact timing of medication initiation was not possible with the VARA registry dataset. Similarly, there was a lack of information on RA medication changes and depressive episodes during follow-up and no data were available regarding depression severity, utilization of antidepressant treatments, and certain comorbid conditions (e.g., fatigue, sleep disturbance). To mitigate this issue, the current study included RA patients with recent disease onset who were prescribed MTX at enrollment. Given that depressed and nondepressed veterans had a disease duration of approximately 7 months, participants represented RA patients with active symptoms who had initiated their first DMARD. Second, administrative diagnostic codes were used to record and measure several study variables, which could potentially introduce misclassification, but any bias would have been nondifferential and trended associations toward the null. In particular, depressive symptoms are often underreported by patients with RA and underrecognized by rheumatologists during routine clinical encounters.^{6,47} Depression may have been underreported and undercoded in the current study sample, and nondifferential misclassification bias could have reduced the magnitude of the observed associations and account for null findings regarding the PtGA and MDHAQ. This contention is supported by the lower-than-expected prevalence ($n = 23$, 8.6%) of posttraumatic stress disorder in the study sample, and

although our estimated depression prevalence compared to the RA population (17.9% vs 16.8%) supports the validity of this measurement approach, prior research indicates that veterans with RA are more likely to develop depression than RA patients without military service.^{5,11} Last, the demographic makeup and occupational exposure history of VARA participants may limit generalizability of the results to other patients (e.g., women).

To conclude, depression in veteran patients with early RA receiving MTX is associated with worse disease activity and more severe and persistent pain, resulting in a less robust treatment response to this cornerstone pharmacological therapy. Thus, this comorbidity may be a risk factor for medication discontinuations, and interventions targeted at treating depression in affected patients with RA could lead to more rapid disease activity control and better DMARD persistence. To facilitate such coordinated medical care, there needs to be routine patient-provider communication about depression, as well as prioritization of psychiatric comorbidity when utilizing treat-to-target medical management for patients with RA.^{6,16} Unfortunately, research indicates a lack of physician awareness about depression and suboptimal communication about depressive symptoms among rheumatologists.⁶ Provider- and/or system-level interventions could improve depression recognition and treatment among patients with RA in large healthcare settings, and, ultimately, augment medical care approaches that utilize multimodal interventions incorporating pharmacologic and nonpharmacologic treatments explicitly designed to address the concurrence of depression and pain in chronic rheumatic diseases.

ACKNOWLEDGMENT

This paper is based on work that was presented previously at the 2019 European League Against Rheumatism (EULAR) Annual Meeting (June 14, 2019; Madrid, Spain) and was published as a conference abstract (Rathbun *et al*, *Ann Rheum Dis* 2019;78:734). This material is based on upon work supported (or supported in part) by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, VA Maryland Health Care System, and Baltimore VA Medical Center. The authors would also like to thank the VA Maryland Health Care System Geriatric Research Education and Clinical Center, VA Office of Academic Affiliations VA Fellowship in Advanced Geriatrics, and many US Veteran patient volunteers who made this work possible.

REFERENCES

1. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum* 2008;58:15-25.
2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010;376:1094-108.
3. 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.
4. Cutolo M, Kitas GD, van Riel PLCM. Burden of disease in treated rheumatoid arthritis patients: going beyond the joint. *Semin Arthritis Rheum* 2014;43:479-88.
5. Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology* 2013;52:2136-48.
6. Rathbun AM, Harrold LR, Reed GW. A description of patient- and rheumatologist-reported depression symptoms in an American rheumatoid arthritis registry population. *Clin Exp Rheumatol* 2014;32:523-32.
7. Löwe B, Willand L, Eich W, Zipfel S, Ho AD, Herzog W, et al. Psychiatric comorbidity and work disability in patients with inflammatory rheumatic diseases. *Psychosom Med* 2004; 66:395-402.
8. Ang DC, Choi H, Kroenke K, Wolfe F. Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:1013-9.
9. Scherrer JF, Virgo KS, Zeringue A, Bucholz KK, Jacob T, Johnson RG, et al. Depression increases risk of incident myocardial infarction among Veterans Administration patients with rheumatoid arthritis. *Gen Hosp Psychiatry* 2009;31:353-9.
10. Pilling S, Anderson I, Goldberg D, Meader N, Taylor C. Depression in adults, including those with a chronic physical health problem: summary of NICE guidance. *BMJ* 2009;339:b4108.
11. Mikuls TR, Padala PR, Sayles HR, Yu F, Michaud K, Caplan L, 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.
12. Overman CL, Bossema ER, van Middendorp H, Wijngaards-de Meij L, Verstappen SM, Bulder M, 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.
13. Rathbun AM, Harrold LR, Reed GW. Temporal associations between the different domains of rheumatoid arthritis disease activity and the onset of patient-reported depressive symptoms. *Clin Rheumatol* 2015;34:653-63.
14. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3-15.
15. Matcham F, Norton S, Scott DL, Steer S, Hotopf M. 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.
16. Rathbun AM, Harrold LR, Reed GW. A prospective evaluation of the effects of prevalent depressive symptoms on disease activity in rheumatoid arthritis patients treated with biologic response modifiers. *Clin Ther* 2016;38:1759-72.
17. Michelsen B, Kristianslund EK, Sexton J, Hammer HB, Fagerli KM, Lie E, et al. Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. *Ann Rheum Dis* 2017;76:1906-10.
18. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res* 2016; 68:1-25.
19. Ng B, Chu A, Khan MM. A retrospective cohort study: 10-year trend of disease-modifying antirheumatic drugs and biological agents use in patients with rheumatoid arthritis at Veteran Affairs Medical Centers. *BMJ Open* 2013;3:e002468.
20. Sergeant JC, Hyrich KL, Anderson J, Kopec-Harding K, Hope HF, Symmons DP, et al. Prediction of primary non-response to methotrexate therapy using demographic, clinical and psychosocial variables: results from the UK Rheumatoid Arthritis Medication Study (RAMS). *Arthritis Res Ther* 2018;20:147.
21. Rohr MK, Mikuls TR, Cohen SB, Thorne JC, O'Dell JR. Underuse of methotrexate in the treatment of rheumatoid arthritis: a national

- analysis of prescribing practices in the US. *Arthritis Care Res* 2017;69:794-800.
22. Mikuls TR, Kazi S, Cipher D, Hooker R, Kerr GS, Richards JS, et al. The association of race and ethnicity with disease expression in male US veterans with rheumatoid arthritis. *J Rheumatol* 2007; 34:1480-4.
 23. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
 24. Mikuls TR, Fay BT, Michaud K, Sayles H, Thiele GM, Caplan L, et al. Associations of disease activity and treatments with mortality in men with rheumatoid arthritis: results from the VARA registry. *Rheumatology* 2011;50:101-9.
 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. Horovitz-Lennon M, Watkins KE, Pincus HA, Shugarman LR, Smith B, Mattox T, et al. Veterans Health Administration mental health program evaluation technical manual. Santa Monica, CA: RAND Health; 2009.
 27. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis clinical trials. *Arthritis Rheum* 1993;36:729-40.
 28. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44-8.
 29. Pincus T, Swearingen C, Wolfe F. Toward a Multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. *Arthritis Rheum* 1999;42:2220-30.
 30. Cordingley L, Prajapati R, Plant D, Maskell D, Morgan C, Ali FR, et al. Impact of psychological factors on subjective disease activity assessments in patients with severe rheumatoid arthritis. *Arthritis Care Res* 2014;66:861-8.
 31. Brydges CR. Effect size guidelines, sample size calculations, and statistical power in gerontology. *Innov Aging* 2019;3:igz036.
 32. England BR, Sayles H, Mikuls TR, Johnson DS, Michaud K. Validation of the rheumatic disease comorbidity index. *Arthritis Care Res* 2015;67:865-72.
 33. Aletaha D, Funovits J, Ward MM, Smolen JS, Kvien TK. Perception of improvement in patients with rheumatoid arthritis varies with disease activity levels at baseline. *Arthritis Rheum* 2009;61:313-20.
 34. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377-99.
 35. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health* 2006; 60:578-86.
 36. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med* 2013;32:3388-414.
 37. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168:656-64.
 38. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; 11:550-60.
 39. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc* 1979;74:829-36.
 40. Iikuni N, Sato E, Hoshi M, Inoue E, Taniguchi A, Hara M, et al. The influence of sex on patients with rheumatoid arthritis in a large observational cohort. *J Rheumatol* 2009;36:508-11.
 41. Kendler KS, Gardner CO. Sex differences in the pathways to major depression: a study of opposite-sex twin pairs. *Am J Psychiatry* 2014;171:426-35.
 42. Brosschot JF, Gerin W, Thayer JF. The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. *J Psychosom Res* 2006;60:113-24.
 43. Adler AB, Castro CA. An occupational mental health model for the military. *Military Behavioral Health* 2013;1:41-5.
 44. Ahlmén M, Svensson B, Albertsson K, Forslind K, Hafström I. Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. *Ann Rheum Dis* 2010;69:230-3.
 45. Barnabe C, Bessette L, Flanagan C, Leclercq S, Steiman A, Kalache F, et al. Sex differences in pain scores and localization in inflammatory arthritis: a systematic review and metaanalysis. *J Rheumatol* 2012;39:1221-30.
 46. Harding K, Day MA, Ehde DM, Wood AE, McCall A, Williams R. Mental and physical health correlates of pain treatment utilization among veterans with chronic pain: a cross-sectional study. *Mil Med* 2019;184:e127-34.
 47. Sleath B, Chewning B, de Vellis BM, Weinberger M, de Vellis RF, Tudor G, et al. Communication about depression during rheumatoid arthritis patient visits. *Arthritis Rheum* 2008; 59:186-91.