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ORIGINAL ARTICLE

Prospective Study of Posttraumatic Stress Disorder and Disease Activity Outcomes in US Veterans With Rheumatoid Arthritis

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Objective. **To examine the relationship between posttraumatic stress disorder (PTSD) and disease activity in US veterans with rheumatoid arthritis (RA).**

Methods. **US veterans with RA were enrolled in a longitudinal observational study and were categorized as having PTSD, other anxiety/depression disorders, or neither of these psychiatric diagnoses using administrative codes. Generalized linear mixed-effects models were used to examine the associations of the diagnostic groups with outcomes measured over a mean followup period of 3.0 years.**

Results. **At enrollment, 1,522 patients had a mean age of 63 years, they were primarily men (91%), and a majority (78%) reported white race. A diagnosis of PTSD was observed in 178 patients (11.7%), and other anxiety/depression diagnoses (excluding PTSD) were found in 360 patients (23.7%). The presence of a PTSD diagnosis was independently associated with higher values of self-reported pain, physical impairment, tender joint count, and worse patient global well-being scores compared to patients with no psychiatric diagnosis. There were no significant group differences in swollen joint count, erythrocyte sedimentation rate, or Disease Activity Score in 28 joints. There were no differences between any outcomes comparing those with PTSD and those with other anxiety/depression diagnoses.**

Conclusion. **In this RA cohort, the diagnosis of PTSD was associated with worse patient-reported outcomes and tender joint counts, but not with other physician- or laboratory-based measures of disease activity. These results suggest that PTSD, along with other anxiety/depression disorders, may affect RA disease activity assessments that rely on patient-reported outcomes and the resulting treatment decisions.**

INTRODUCTION

Posttraumatic stress disorder (PTSD) represents a specific form of anxiety disorder that develops following the exposure to an event resulting in marked psychological trauma. PTSD is characterized by persistent reexperiencing of the traumatic event, in addition to avoidance of stimuli associated with the trauma, numbing of general responsiveness, and persistent symptoms of increased arousal (1). As a result of these symptoms, PTSD exerts a major negative impact on health-related quality of life. The lifetime prev-

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Significance & Innovations

- This is the first comprehensive study examining the impact of posttraumatic stress disorder (PTSD) on measures of disease activity in rheumatoid arthritis (RA).
- These results show that PTSD exerts a significant detrimental effect over time on patient-reported outcomes in RA, including pain, physical functioning, and patient global well-being scores, in addition to tender joint counts. Similar effects were not observed for swollen joint counts, erythrocyte sedimentation rate, or physician global assessment scores.
- These results suggest that PTSD, along with other anxiety/depression disorders, may inform treatment decisions that are based on the use of tender joint counts and other patient-reported outcome measures of RA disease activity.

alence of PTSD in the general population is estimated to approach 5%, although its frequency has been reported to exceed 40% in inner-city dwellers prone to disproportionately higher exposure to violent crime (2,3). PTSD is a major source of morbidity among US military veterans. Among Vietnam veterans, PTSD prevalence has been estimated to be between 15% and 31% (4,5), and for Gulf War veterans, the prevalence estimates range from 5–12% (6,7). With more recent military operations, including Operation Iraqi Freedom and Operation Enduring Freedom, the burden of PTSD in returning veterans appears to be equal to or even higher than that observed among Vietnam veterans (8,9).

There is an increasing awareness that veterans experiencing PTSD are affected with disproportionately higher rates of other chronic illnesses, including cardiovascular disease, diabetes mellitus, psoriasis, gastrointestinal diseases, and rheumatoid arthritis (RA) (10–15). Using a cotwin design, Boscarino and colleagues recently reported that the presence of PTSD symptoms was independently associated with RA (14). Preliminary studies suggest that prevalent PTSD may actually increase the risk of developing RA (11,14). In addition to a greater comorbidity burden with physical illnesses including RA, veterans with PTSD from all combat theaters are known to report higher rates of pain, pain-related disability, and functional impairment (16–18). In a study of outpatient veterans with PTSD, a majority of participants (80%) satisfied the criteria for chronic pain (19). The reverse is also true; patients experiencing chronic musculoskeletal pain are 4 times more likely to have PTSD than those without musculoskeletal pain (20). Despite the known detrimental effect of PTSD on pain and physical function, both of which are core outcome domains in RA, there have been no prior investigations examining the impact of PTSD on measures of RA-related clinical status.

In this study, we sought to examine the associations of PTSD with the measures most commonly used to characterize disease activity in RA. We hypothesized that among a well-characterized cohort of US veterans with RA, a diagnosis of PTSD would be associated with measures reflecting more active disease, in particular, higher levels of self-reported pain and worse physical functioning, compared to those without a PTSD diagnosis. We examined the relationship of PTSD with the core measures of RA disease activity at the time of study enrollment and further examined the association of PTSD with clinical status assessed longitudinally over an extended period of observation.

PATIENTS AND METHODS

Participants and procedures. The study participants included US veterans enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) registry (21,22). The VARA registry is a multicenter chronic disease registry and biorepository that involved active collection sites at 9 VA rheumatology clinics across the US at the time of this study. All study participants satisfied the 1987 American College of Rheumatology classification criteria for RA (23) and provided informed consent prior to registry enrollment. The study was approved by an institutional review board at each participating center and was approved by the VARA Scientific and Ethics Advisory Committee.

Measures. Administrative diagnostic codes (International Classification of Diseases, Ninth Revision [ICD-9]) were obtained for the study participants by merging the VARA registry with data from the national VA Decision Support System (DSS) (24). PTSD was defined based on the presence of at least 1 ICD-9 code of 309.81 occurring anytime during the receipt of VA care preceding the last registry observation prior to October 1, 2011. To mitigate a possible detection bias related to recent VA-wide efforts of identifying PTSD cases (25), psychiatric diagnoses were assumed to exist prior to registry enrollment. Our study included a large proportion of Vietnam veterans with a mean age of >60 years, and studies have consistently suggested that the majority of these veterans developed PTSD from exposure to combat decades ago and would therefore represent chronic cases of PTSD (10–13). The positive predictive value of ICD-9 code 309.81 has previously been shown to be between 75% and 82%, with the latter value based on the presence of 2 ICD-9 codes of 309.81 separated in time (26). To compare the relative impact of PTSD with the effect of other common psychiatric diagnoses, patients were also categorized based on the presence of at least 1 diagnostic code corresponding to an alternative anxiety or depression disorder. The alternative anxiety disorders examined included unspecified anxiety state (300.00), panic disorder (300.01), generalized anxiety disorder (300.02), and adjustment reaction (309* excluding 309.81). The depression diagnoses examined included major depressive disorder (296.2 to 296.36), other unspecified episodic mood disorder (296.90), and depressive disorder not otherwise classified (311*). In the absence of any of the aforementioned diagnostic codes, patients were categorized as having no psychiatric diagnosis. Other psychiatric diagnoses less frequently repre-

sented in this cohort, such as psychosis and bipolar disorder, were not applied as exclusion criteria, nor were these considered further as covariates of interest.

Medications and all American College of Rheumatology core measures of RA disease activity (27) were recorded in the VARA registry at the time of each rheumatology encounter. The medications recorded included glucocorticoids (e.g., prednisone) and all biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs). The measures of disease activity assessed included both physician- and patient-reported outcomes, recognizing the complementary nature of these assessments as part of a comprehensive approach to RA management. The longitudinal measures of disease activity collected in the VARA registry included the Multidimensional Health Assessment Questionnaire (MD-HAQ; range 0–3), self-reported pain (range 0–10), tender and swollen joint counts (range 0–28), erythrocyte sedimentation rate (ESR; in mm/hour), and separate 100-mm visual analog scales of patient and provider global well-being (with 0 corresponding to doing as well as possible and 100 corresponding to doing as poorly as possible). Disease Activity Score in 28 joints values were calculated for each encounter. Other variables collected at the time of the registry enrollment included age, age at disease onset, sex, race, and smoking status (never, former, and current). A medical comorbidity count was calculated for each patient using administrative diagnostic codes from the DSS (a compilation of cardiovascular disease, cerebrovascular accident, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, chronic obstructive pulmonary disease, or interstitial lung disease [range 0–8]). Anti–cyclic citrullinated peptide (anti-CCP) antibody was measured on banked serum collected at enrollment using DIASTAT (Axis-Shield Diagnostics), a second-generation enzyme-linked immunosorbent assay (positivity ≥5 units/ml) (22). Rheumatoid factor was determined by nephelometry (Siemens Healthcare Diagnostics; positivity ≥15 IU/ml) (22).

Statistical analysis. Comparisons of the patient characteristics were examined by psychiatric diagnostic group using the chi-square test for dichotomous variables and analysis of variance (ANOVA) for continuous variables. Unadjusted comparisons of the 8 continuous core disease activity measures assessed at study enrollment were examined using one-way ANOVA, accounting for 3-group comparisons using the Tukey-Kramer post hoc test. For all comparisons, ESR was log transformed to render a normal distribution. Given skewed distributions, both tender and swollen joint counts were dichotomized into 2 categories, 0 tender/swollen joints and ≥1 tender/swollen joints, with comparisons examining the probability of having a joint count >0. Actual continuous joint counts were also reported for descriptive purposes. Effect sizes were calculated by dividing the group mean differences by the pooled SD for the measure. We defined small effect sizes as 0.2, moderate as 0.5, and large as 0.8, per Cohen's criteria (28). To account for the 8 outcomes being examined, statistical significance was defined conservatively as a *P* value less than 0.00625 (0.05 divided by 8) in both univariate and multivariable models.

Subsequent analyses were then completed to examine whether the relationship observed between PTSD and RA clinical status at enrollment was independent of other covariates, and to examine whether this relationship was apparent over an extended period of longitudinal observation (mean of 3 years). Generalized linear mixed-effects (GLIMMIX) models were used to examine the multivariable associations of psychiatric diagnostic group (PTSD, other diagnoses, and no psychiatric diagnoses) with RA clinical status assessed over study followup. The models were adjusted for factors, including age, sex, RA disease duration, smoking status at enrollment, comorbidity count, anti-CCP antibody positivity at enrollment, race (white versus other), and medication use (methotrexate, prednisone, and any biologic agent at the time of the previous clinic visits). The GLIMMIX models were used to adjust for the random effects from clinical sites and the correlation between the RA outcome measures from the same patient via compound symmetry correlation structure. Patients from 3 sites were excluded from the multivariable analysis due to the small total number of RA patients enrolled from these centers (n = 93). A normal distribution was assumed for the continuous outcome measures examined, with the exception that a Bernoulli distribution was assumed for the categorized tender and swollen joint counts. When medication data were missing for a given clinical visit, values from the previous clinical visit were used for imputation. The adjusted mean RA outcome measures or the probability of having positive tender or swollen joint counts over time was estimated and compared among the 3 groups. The Tukey-Kramer post hoc test was again used to account for simultaneous comparisons between the 3 diagnostic groups. Additional sensitivity analyses were undertaken to examine the impact of limiting PTSD cases to those with 2 or more corresponding diagnostic codes separated in time (26). In additional sensitivity analyses, we also explored the impact of having a diagnosis of both comorbid PTSD and depression or an alternative anxiety disorder on RA clinical status using the same statistical approach. All analyses were completed using Stata.

RESULTS

There were 1,522 US veterans with RA included in the analysis, with longitudinal data encompassing 14,942 observations and 4,567 cumulative patient-years of followup (mean followup of 3 years). The RA patient characteristics are shown in Table 1. At the time of registry enrollment, patients had a mean age of 63 years, were predominantly men (91%), and most frequently self-reported white race (78%). Of the 1,522 patients examined, 178 (11.7%) had at least 1 ICD-9 code for PTSD (309.81), a majority of whom also had a concomitant diagnosis of depression (n = 145), with a smaller proportion having a concomitant alternative anxiety diagnosis (n = 65). Other anxiety or depression diagnoses, excluding PTSD, were coded in 360 patients (23.7%). Requiring 2 separate dates with the recorded ICD-9 code of 309.81 yielded 132 PTSD cases

Table 1. Characteristics of RA patients at the time of study enrollment*

	Total (n = 1,522)†	No psychiatric diagnosis (n = 984)	PTSD (n = 178)	Anxiety/depression without PTSD (n = 360)
Sociodemographics				
Age, mean ± SD years‡	63.2 ± 11.5	64.5 ± 11.7	58.8 ± 8.0	61.8 ± 11.6
Men	90.8	91.6	90.5	88.9
White	77.6	78.5	70.8	78.6
≥HS education	84.2	84.3	87.4	82.3
Other factors				
Comorbidity count, mean ± SD‡	1.8 ± 1.6	1.6 ± 1.5	2.3 ± 1.7	2.2 ± 1.7
Smoking status‡				
Never	20.7	21.9	15.2	20.0
Former	51.8	54.0	39.9	51.7
Current	27.5	24.1	44.9	28.3
RA prognostic factors				
Disease duration, mean ± SD years	11.2 ± 11.4	11.5 ± 11.6	9.9 ± 10.3	10.8 ± 11.4
RF positive	80.6	80.2	81.6	80.9
Anti-CCP positive	75.7	75.9	75.7	75.2
Prednisone	42.8	42.0	46.9	43.2
Methotrexate	51.2	52.7	50.0	47.8
Biologic agent	22.1	22.7	23.1	20.2
Age at diagnosis, mean ± SD years‡	52.0 ± 14.1	52.9 ± 14.6	49.0 ± 11.5	51.0 ± 13.6

* Values are the percentage unless otherwise indicated. RA = rheumatoid arthritis; PTSD = posttraumatic stress disorder; HS = high school (12 years); RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide.
† The median values for continuous variables are as follows: total: age 63 years (range 19–90 years), comorbidity 2 (range 0–7), disease duration 8 years (range 0–62 years), age at diagnosis 53 years (range 18–90 years); no diagnosis: age 65 years (range 19–90 years), comorbidity 1 (range 0–7), disease duration 8 years (range 0–61 years), age at diagnosis 54 years (range 18–90 years); PTSD: age 58 years (range 35–88 years), comorbidity 2 (range 0–7), disease duration 7 years (range 0–50 years), age at diagnosis 51 years (range 18–90 years); anxiety/depression: age 62 years (range 25–90 years), comorbidity 2 (range 0–7), disease duration 7 years (range 0–62 years), age at diagnosis 52 years (range 18–82 years).
‡ $P \leq 0.001$ for differences by diagnostic group (all other P values > 0.05); P values were generated as a global test for differences across groups using the chi-square test for categorical variables and one-way analysis of variance for continuous variables.

(8.7%). The patient characteristics were similar by psychiatric diagnostic group, with the exception that PTSD patients were slightly younger, more likely to smoke (current or ever), and younger at RA onset compared to the other patient groups. Compared to those without a psychiatric diagnosis, those with PTSD and those with other anxiety/depression diagnoses had more comorbid illness.

The results of the univariate analyses examining the associations of the 3 diagnostic groups with RA outcome measures at the time of enrollment are shown in Table 2.

Table 2. Mean measures of disease activity in rheumatoid arthritis patients at the time of study enrollment by diagnostic group*

	No psychiatric diagnosis	PTSD	Other anxiety/depression
Pain score (range 0–10)†	4.0 ± 2.8	5.4 ± 2.5	5.0 ± 2.8
MD-HAQ (range 0–3)†	0.9 ± 0.6	1.2 ± 0.6	1.1 ± 0.6
Tender joints (range 0–28)‡	3.1 ± 5.4	5.4 ± 7.7	4.3 ± 6.2
Swollen joints (range 0–28)	2.5 ± 4.2	3.2 ± 4.9	2.9 ± 4.5
Patient global (range 0–100)†	37.5 ± 25.1	48.4 ± 23.9	45.8 ± 24.8
Provider global (range 0–100)†	28.8 ± 21.2	35.1 ± 21.4	34.7 ± 23.2
ESR, mm/hour§	27.8 ± 23.7	23.9 ± 21.3	27.5 ± 23.2
DAS28¶	3.4 ± 1.4	3.7 ± 1.5	3.8 ± 1.5

* Values are the mean ± SD. Group comparisons used transformation of the outcome variable (joint counts were dichotomized as 0 versus >0 and ESR was log transformed). Statistical significance was defined as $P < 0.00625$. PTSD = posttraumatic stress disorder; MD-HAQ = Multidimensional Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score in 28 joints.
† $P < 0.001$ for PTSD versus no psychiatric diagnosis and for other anxiety/depression versus no psychiatric diagnosis.
‡ $P = 0.07$ for PTSD versus no psychiatric diagnosis and $P = 0.009$ for other anxiety/depression versus no psychiatric diagnosis.
§ $P = 0.01$ for PTSD versus no diagnosis and $P = 0.02$ for PTSD versus other anxiety/depression.
¶ $P = 0.09$ for PTSD versus no psychiatric diagnosis and $P = 0.003$ for other anxiety/depression versus no psychiatric diagnosis.

Table 3. Multivariable associations of PTSD with measures of disease activity in RA patients over followup*

	PTSD vs. no psychiatric diagnosis		Other anxiety/depression vs. no psychiatric diagnosis		PTSD vs. other anxiety/depression	
	β coefficient	*P*	β coefficient	*P*	β coefficient	*P*
Pain score (range 0–10)	0.96	< 0.0001	0.75	< 0.0001	0.20	0.55
MD-HAQ (range 0–3)	0.22	< 0.0001	0.17	< 0.0001	0.05	0.59
Tender joints (0 vs. >0)	0.46	0.0002	0.33	0.0007	0.14	0.51
Swollen joints (0 vs. >0)	−0.01	1.00	−0.11	0.46	0.10	0.73
Patient global (0–100-mm scale)	8.76	< 0.0001	6.93	< 0.0001	1.83	0.57
Provider global (0–100-mm scale)	3.77	0.03	5.03	< 0.0001	−1.27	0.71
Log ESR, mm/hour	−0.14	0.20	0.01	0.96	−0.15	0.18
DAS28	0.27	0.03	0.29	0.001	−0.02	0.98

* Mean followup of 3 years. Adjusted for age, sex, rheumatoid arthritis (RA) disease duration, smoking status at enrollment, comorbidity count, anti–cyclic citrullinated peptide positivity at enrollment, race (white versus other), and medication use including methotrexate, prednisone, and any biologic agent at the time of the clinic visit. The analyses account for clustering by 6 study sites. *P* values adjusted for 3 diagnostic groups using the Tukey-Kramer post hoc test. Swollen and tender joint counts were examined as binary values (equal to 0 or >0). Statistical significance was defined as $P < 0.00625$. PTSD = posttraumatic stress disorder; MD-HAQ = Multidimensional Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score in 28 joints.

Compared to patients without a psychiatric diagnosis, those with PTSD exhibited significantly higher values for pain (effect size 0.51), MD-HAQ (effect size 0.41), patient global well-being (effect size 0.44), and provider global well-being (effect size 0.29) scores at the time of study enrollment. There was no significant difference in tender joint count in patients with PTSD compared to those with no psychiatric diagnosis (effect size 0.38, $P = 0.07$). The associations of other anxiety/depression diagnoses with RA outcomes were generally similar to those observed for PTSD. There were no significant differences in any of the outcomes between those with PTSD and those with other psychiatric diagnoses.

Subsequent multivariate analyses were conducted to examine the associations of PTSD with RA clinical status over time, adjusting for the aforementioned confounders and accounting for multiple outcomes (Table 3). In adjusted analyses, PTSD was associated with significantly higher values of self-reported pain, MD-HAQ, tender joint count, and worse patient global well-being scores compared to patients with no psychiatric diagnosis. For example, after adjusting for important confounders and when compared to patients without a psychiatric diagnosis, a diagnosis of PTSD was associated with a pain score that was a mean of ~1 unit higher when using a 1–10 scale over followup ($\beta = 0.96$, $P < 0.0001$). As seen in the univariate analyses, there were no significant differences in outcomes between those with PTSD and those with other anxiety/depression disorders. These results were not changed in sensitivity analyses when PTSD case status was defined as those having at least 2 diagnostic codes separated in time (Table 4). The effects of concomitant PTSD with an alternative anxiety or depression diagnosis were similar to those observed with PTSD in the primary analyses (Table 4).

Table 4. Results of sensitivity analyses: multivariable PTSD with RA clinical status over followup*

	Model 1: PTSD (2 ICD-9 codes) vs. no psychiatric diagnosis		Model 2: PTSD plus depression vs. no psychiatric diagnosis		Model 3: PTSD plus other anxiety disorder vs. no psychiatric diagnosis	
	β coefficient	*P*	β coefficient	*P*	β coefficient	*P*
Pain score (range 0–10)	0.93	< 0.0001	1.04	< 0.0001	0.92	0.002
MD-HAQ (range 0–3)	0.25	< 0.0001	0.25	< 0.0001	0.16	0.05
Tender joints (0 vs. >0)	0.49	0.0005	0.57	< 0.0001	0.50	0.02
Swollen joints (0 vs. >0)	0.004	1.00	0.0005	1.00	−0.11	0.85
Patient global (0–100-mm scale)	8.64	< 0.0001	9.86	< 0.0001	11.02	< 0.0001
Provider global (0–100-mm scale)	4.29	0.03	5.51	0.004	3.80	0.20
Log ESR, mm/hour	−0.15	0.21	−0.13	0.31	−0.05	0.90
DAS28	0.26	0.08	0.33	0.02	0.34	0.08

* Mean followup of 3 years. Each model was adjusted for age, sex, rheumatoid arthritis (RA) disease duration, smoking status at enrollment, comorbidity count, anti–cyclic citrullinated peptide positivity at enrollment, race (white versus other), and medication use including methotrexate, prednisone, and any biologic agent at the time of clinic visit. The analyses account for clustering by 6 study sites. *P* values adjusted for 3 diagnostic groups using the Tukey-Kramer post hoc test (comparisons of PTSD versus other diagnosis and other diagnosis versus no psychiatric diagnosis not shown for each model). Swollen and tender joint counts were examined as binary values (equal to 0 or >0). Statistical significance was defined as $P < 0.00625$. PTSD = posttraumatic stress disorder; ICD-9 = International Classification of Diseases, Ninth Revision; MD-HAQ = Multidimensional Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score in 28 joints.

DISCUSSION

In this cohort, PTSD affected ~12% of US veterans with RA. The presence of a PTSD diagnosis was independently associated with worse RA clinical status over an extended period of followup. Specifically, patients with RA and comorbid PTSD demonstrated higher levels of pain, increased levels of functional impairment, higher tender joint counts, and worse patient global well-being scores compared to RA patients without PTSD and alternative anxiety/depression disorders. The absence of a demonstrable association with ESR suggests that the mechanism by which PTSD exerts its detrimental impact on RA disease course is likely not due to any proinflammatory effect. Importantly, the outcomes impacted by PTSD are frequently used clinically, either alone or as components of composite indices, to quantify ongoing disease activity in RA and ultimately to gauge treatment response to DMARDs and other antiinflammatory agents (29). Our results suggest that comorbid PTSD may confound many of these disease activity assessments. If the detrimental impact of PTSD on RA patient–reported outcomes is independent of inflammatory mechanisms, as our results suggest, then the use of these measures to guide the initiation or escalation of therapies that primarily target inflammatory pathways may be fraught with problems. Given the central importance of patient-reported outcomes including pain and physical functioning as part of any comprehensive treatment approach, clinicians providing care for RA patients with comorbid PTSD may need to consider alternative means of therapy, such as counseling or agents proven to ameliorate the signs and symptoms of PTSD.

The diagnosis of PTSD appears to be most strongly associated with greater pain, joint tenderness, and functional impairment in RA relative to patients without anxiety, depression, or PTSD. Recognizing that the minimum clinically important difference in pain has been defined as a 0.5–1.1-unit change on a 0–10 scale (30), the deleterious impact that PTSD exerted in this study (approaching 1 unit) underscores the relevance of these findings among patients with RA. The difference in self-reported pain symptoms among those with PTSD compared to those with no psychiatric diagnosis is similar in magnitude to improvements in pain attributed to the receipt of biologic anti–tumor necrosis factor therapy in RA (30). The associations of PTSD with greater pain and worse functional ability may have added relevance, since these outcomes strongly influence overall health status in RA patients (31). Moreover, of all the core measures examined in our study, higher levels of patient-reported functional impairment are among the strongest predictors of 5-year mortality in RA (32).

The associations of PTSD with patient outcomes in the present study were similar to those observed for other anxiety disorders and depression. Our results do not support the existence of a synergistic effect of comorbid psychiatric diagnoses (e.g., PTSD plus depression) on RA clinical status, which was not expected. However, these results imply that PTSD and the other psychiatric conditions examined could affect musculoskeletal disease outcomes through similar pathways that have yet to be fully elucidated. Although we were not able to assess such factors in the present study, it is possible that discrepancies in these outcomes could be due to individual differences in the frequency of poor health behaviors among those experiencing PTSD. Patients with PTSD, for example, are 80% more likely to report medication nonadherence and are 70% more likely to report skipping medications compared to those without PTSD (33). Although several theories have been proposed for increased musculoskeletal pain symptoms in PTSD, perhaps the most accepted theory is the shared vulnerability model (16). In this model, it is proposed that a shared and heightened sensitivity to anxiety exists in both PTSD and musculoskeletal diseases. The potential mechanisms underpinning the associations of PTSD, other anxiety disorders, and depression with other RA outcomes observed in this study have not been well defined.

There are limitations to this study. Our sample was limited to US veterans, a population that is unique relative to other RA populations because it is predominantly comprised of older men. Further, the limited number of ethnic minority patients within specific diagnostic categories prohibited meaningful assessments referent to these important populations. Therefore, these results may not be generalizable to other populations, particularly women, who account for the largest demographic group affected by RA. Our reliance on administrative diagnostic codes for case identification introduced the possibility of misclassification (26), which would likely bias these results toward the null and render our results into conservative estimates of the associations examined. Recently, VA researchers have recommended the use of 2 ICD-9 309.81 codes separated in time as a means of optimizing the predictive value of code-based case definitions for PTSD (26). However, use of this definition did not alter our results, but it did decrease the size of our case group by >25%. Although recent quality improvement efforts in the VA Health System have emphasized systematic screening for PTSD along with appropriate psychiatric referral for those who screen positive (25), we were not able to capitalize on these screening results, since this screening initiative was not systematically adopted by VA facilities until 2008. The prevalence of PTSD observed in our study is similar to another study involving veteran populations (34), and it is higher than another investigation conducted in the VA that also used only ICD-9 codes for case identification (35). We cannot definitively exclude the possibility of a referral bias leading to lower registry enrollment of RA patients with PTSD compared to those without PTSD, although the frequency of PTSD observed would suggest that this was unlikely. Although this study provided a mean followup period of 3 years, longer durations of observation will be necessary to better define the complex interrelationship of PTSD with RA. While the focus of this study was the impact of comorbid PTSD on RA outcomes, it is quite possible that RA may impose equally detrimental effects on PTSD in terms of both its occurrence and prognosis. This knowledge gap will need to be addressed in future studies.

There are also important strengths to this study. To our knowledge, this is the first study to examine the associa-

tions of PTSD, a substantial and growing health problem, with disease-related outcomes in patients with RA. The VA currently represents the single largest integrated health system in the US, and with the potential socioeconomic barriers to health care access either removed or mitigated, it provides an ideal context for the study of disease outcomes. The VA is a particularly ideal context for the study of PTSD, given the ongoing initiatives within the VA Health System to identify and treat mental health problems among its veteran beneficiaries (25). The additional strengths of this study include the availability of a large, well-characterized cohort of veterans with RA, all of whom have been diagnosed in the context of rheumatology subspecialty care. The VARA database, with its links to national VA data and a biorepository, provides unique access to a diverse number of covariates that could directly impact disease-related outcomes.

Interventions could be tailored to improve outcomes specifically for patients with comorbid PTSD and RA. For instance, cognitive–behavioral therapy has been shown to improve outcomes in patients with chronic pain, including reductions in self-reported pain experience and improved coping behaviors (36). Such interventions could be used to optimize patient outcomes in RA patients affected by PTSD while minimizing exposure to other potentially toxic, costly, and perhaps unnecessary therapies. Delineating the many pathways that are likely to link PTSD with poor outcomes in RA poses a formidable challenge. Additional insights in this area may provide avenues for improved management of pain, physical functioning, and quality of life in a significant and growing proportion of RA patients.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mikuls had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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