A Twin Study of the Association Between PTSD Symptoms and Rheumatoid Arthritis

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Objectives: To assess the association between posttraumatic stress disorder (PTSD) and rheumatoid arthritis (RA) and to determine if this was due to PTSD or confounding by environmental and genetic factors. **Methods:** Data were obtained from 3143 twin pairs in the Vietnam Era Twin Registry, which included male twin pairs who served during the Vietnam War era (mean age, 40.6 years; standard deviation, 2.9). Measurements included a PTSD symptom scale, history of physician-diagnosed RA, sociodemographics, and health confounding factors. Co-twin control analytic methods used generalized estimating equation logistic regression to account for the paired twin data and to examine the association between PTSD symptoms and RA in all twins. Separate analyses were conducted within twin pairs. **Results:** The prevalence of RA among this population was 1.9% (95% confidence interval, 1.6–2.3) and the mean PTSD symptom level was 25.5 (standard deviation, 9.6). PTSD symptoms were associated with an increased likelihood of adult RA even after adjustment for confounding ($p_{trend} < .001$). Among all twins, those in the highest PTSD symptom quartile were 3.8 times more likely (95% confidence interval, 2.1–6.1) to have RA compared with those in the lowest. These findings also persist when examined within twin pairs ($p_{trend} < .022$). **Conclusions:** PTSD symptoms were associated with adult RA onset. Even after adjustment for familial/genetic factors and other confounders, an association between PTSD symptoms and RA remained. This is one of the first studies to demonstrate a link between PTSD and RA onset among a community-based population sample, independent of familial and genetic factors. **Key words:** posttraumatic stress disorder, rheumatoid arthritis, autoimmune disease, inflammation, zygosity, co-twin study.

PTSD = posttraumatic stress disorder; **RA** = rheumatoid arthritis; **VET** = Vietnam Era Twin; **GEE** = generalized estimating equation; **MZ** = monozygotic; **DZ** = dizygotic; **BMI** = body mass index.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a disabling mental health disorder affecting those exposed to traumatic events and is associated with reexperiencing, avoidance, and hyperarousal symptoms related to such events (1,2). Recent research (3–5) has suggested that having PTSD was associated with an increased prevalence of chronic diseases, including cardiovascular and autoimmune diseases (6,7). There are several clinical reasons to expect a link between PTSD and rheumatoid arthritis (RA). First, research (6–9) has suggested that PTSD may result in inflammatory injuries through overactivation of the hypothalamic-pituitary-adrenocortical and sympathetic-adrenal-medullary stress axes, subsequently followed by hypocortisolism related to molecular down-regulation of these systems. Although the pathophysiology of hypocortisolism is complex (8), it has been hypothesized that this persistent state could increase inflammation and inflammatory-related diseases (7,10). Consistent with this hypothesis, research (11,12) has suggested the presence of low-grade systemic proinflammation activity in PTSD cases. Furthermore, current RA research (13) suggested that dysregulation of reciprocally controlled mechanisms involving neuroendocrine, immune, endothelial, and neural systems may trigger RA onset. In addition to the above pathophysiology, this disease link could be due to shared physiologic mechanisms, such as inadequate adrenal functioning, which could be associated with both psychological reactions to environmental stressors and biologic vulnerability to disease (6). This link also could have occurred through altered health behaviors, such as heavy cigarette smoking related to self-regulation of aversive psychological states, brought on by PTSD psychopathology (6,14). Another possibility was that this association could be due to self-selection, whereby those who developed PTSD and RA might have certain character traits that were related to both exposure to psychological trauma and the onset of disease (6).

Studies (7,15,16) suggesting a link between PTSD and RA are limited. There is only one community-based study that reported a positive association between PTSD and RA, but this study (7) did not control for familial or genetic factors. To date, studies have documented the role of genetic risk factors in both RA (17,18) and PTSD (19,20). In addition, research (4,6–8,15,16) has identified at least one candidate environmental factor that might contribute to both PTSD and RA—specifically, exposure to psychological trauma. In particular, there is a documented link between exposure to psychological trauma earlier in life and increased risk of RA in adulthood (7,8,15,16). The biologic plausibility of this link is related to evidence of hypothalamic-pituitary-adrenocortical axis and related neuroendocrine-immune system dysregulation after traumatic stress exposures and the suspected pathophysiology of RA onset involving these systems (6–13,16).

The purpose of this co-twin study is to examine the association between PTSD symptoms and RA in Vietnam era veterans. Co-twin studies allow investigators to separate the effects of familial and genetic factors through examination of associations of interest among monozygotic (MZ) and dizygotic (DZ) twins. Specifically, in the current study, we determined: 1) if PTSD symptoms were associated with the onset

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of RA; and 2) if the association between PTSD and RA was due to the influence of common genetic or environmental factors.

METHODS

Sample and Setting

The Vietnam Era Twin (VET) Registry is a large, closed, national sample of twins in the United States assembled in the mid-1980s by a systematic search of the Department of Defense military records and Department of Veterans Affairs benefit records (21). Twins eligible for the VET Registry are male-male twin pairs, born between 1939 and 1957, both of whom served on active military duty during the Vietnam War era (defined as May 1965 to August 1975). A total of 7375 male-male twin pairs were identified and were subsequently contacted for inclusion in the VET Registry. In 1987, an initial mail and telephone survey of all twin pairs was administered to determine general health status, combat exposure, and symptoms of PTSD. A total of 4774 complete twin pairs responded to this initial survey, a 65% pair-wise response rate.

A second mail and telephone survey, conducted in 1991, further assessed physical health disorders and included questions about RA. In total, 3698 complete twin pairs responded to the 1991 survey (22).

The current analysis includes twin pairs who both responded to the 1987 and 1991 surveys and have complete data for PTSD and RA. A total of 3143 twin pairs met these criteria for study inclusion. As our overall study completion rate was <50%, we comment on this limitation in the discussion section of this paper. This study was approved by the VA Puget Sound Health Care System Institutional Review Board, Seattle, Washington.

Measurement of PTSD and Adult RA

PTSD was assessed in the 1987 survey, using 15 questions about the frequency of PTSD symptoms in the last 6 months. The questionnaire items encompassed the same PTSD symptom criteria (e.g., reexperiencing, avoidance, and hyperarousal) included in the Diagnostic and Statistical Manual of Mental Disorders, *Third Edition* (23). These symptom questions are similar to those used in the PTSD Checklist (24) and Mississippi scale (25) of PTSD and were developed from previous PTSD research (26). For this PTSD scale, subjects indicated symptom frequency on a four-level ordinal response, ranging from very often = 4 to never = 1. The sum of the 15 items forms the PTSD symptom scale used in this study (mean, 25.5; standard deviation [SD], 9.6; median, 23; range, 15–74; skewness, 1.3; kurtosis, 4.8). We grouped the PTSD symptom score into quartiles, ranging from those with the lowest frequency of PTSD symptoms (the first quartile) to the highest (the fourth quartile). We also use this scale as a continuous measure. This scale has been used in previous investigations and has been demonstrated to have both good concurrent (20,26) and predictive validity (6). This scale has been shown to be comparable with results obtained using the Diagnostic Interview Schedule (5,6). Finally, Cronbach's α was reported to be high for these PTSD scale items ($\alpha = 0.92$) (5), as was the Guttman split-half coefficient (0.91) (5), suggesting good internal reliability.

The diagnosis of RA was obtained 4 years after the 1987 survey as part of the 1991 follow-up survey. The specific RA questions included the item: ''Has a doctor ever told you that you have rheumatoid arthritis?" If the response to this question was "yes," the twin was asked: "At what age did you first have this condition?" Those who reported RA occurred at age ≥21 years were defined as adult-onset RA cases. Because this was a veteran population with wartime military service, persons with preservice RA, as well other serious medical conditions, would be systematically and routinely excluded from military service (3). Also, self-reported measures of physician-diagnosed chronic diseases are commonly used in health surveys and have been reported to be reasonably accurate measures for most chronic conditions, including history of depression (3,27).

Confounding Factors

A number of potential confounding factors were available from the 1987 and 1991 surveys. These self-report variables included: age, highest year of education attained, body mass index (BMI), cigarette smoking history, a combat exposure measure (28), and a self-reported question on history of the diagnosis of depression by a doctor. It is noted that the combat exposure measure used has been previously validated (28) and used in other veteran studies as well (6,20,26). Zygosity was determined, using a questionnaire-based prediction algorithm from childhood similarity and supplemented with deoxyribonucleic acid data available from the VET Registry (21).

Statistical Analysis

Initial analysis examined the distribution of risk and confounding factors in those with and without RA. We estimated the prevalence of RA and accompanying 95% confidence intervals (CIs) according to quartiles of the PTSD symptom score. Formal statistical analysis examined the association of PTSD symptoms and RA at the same time taking into account the paired structure of the data. For this, we used generalized estimating equation (GEE) logistic regression models with the twin pairs defined as the clusters. The strength of the association between PTSD symptoms and RA was estimated by odds ratios (ORs) and 95% CIs. The PTSD and RA association was examined with and without adjustment for potential sociodemographic and health confounding factors. We repeated a similar analysis estimating the within-pair association of PTSD symptoms with RA. This within-pair analysis controls for numerous familial/genetic factors that could be confounders and is superior to covariate-adjusted statistical modeling (29). This is achieved though the co-twin, within-pair, GEE linear regression analysis that controls for common familial and heritability factors captured in these data. Specifically, the within-pair effect is measured by each twin's difference from the mean score of the twin pair. The twin pair's mean score is used to estimate the between-pair effect. Details of how twin data can be reparameterized into separate within-pair and between-pair components can be found in the study by Carlin and colleagues (29). The linear trend of the association between PTSD symptom score quartiles and RA diagnosis was accessed, using the continuous PTSD symptom score, or the continuous within-pair component of PTSD symptom score through GEE linear regression. We do not present data stratified by zygosity, because the number of RA cases was generally considered too small to obtain reliable statistical estimates separately for MZ and DZ pairs given the number of predictors used (30). Age and BMI were coded as continuous measures. Education was used as a 5-point ordinal scale coded from less than high school to graduate school. Smoking status was coded as a 3-categorical measure representing never, former, and current smoker. Combat exposure was used as a 4-point ordinal scale ranging from no Vietnam service or no combat, to men who were exposed to high combat. Finally, history of depression was coded as a binary variable. All analyses were conducted using Stata, version 9.2 (College Station, Texas).

RESULTS

The overall prevalence of RA in the VET Registry as of 1991 was 1.9% (95% CI, 1.6–2.3) (Table 1). The prevalence was similar in both MZ and DZ pairs. No significant difference was found for the mean age of the cohort (mean, 40.6; SD, 2.9) by RA status ($p = .899$). This was also true for mean BMI ($p = .662$). However, the prevalence of RA varied by education, with those having less than a high school education having a higher prevalence than those who attended college/graduate school ($p = .015$). Although smoking status was found to be nonsignificant by RA status ($p = .127$), the prevalence of RA was higher among twins with medium and high combat exposure compared with twins with either no or low levels of combat exposure ($p = .009$). In addition, for those with a doctor's diagnosis of depression, the prevalence of RA was significantly elevated compared with those without this diagnosis ($p < .001$). Also, those with a diagnosis of adult-onset RA had significantly higher PTSD symptoms (mean, 33.5; SD, 13.5), compared with those without adult RA (mean, 25.4; SD, 9.4) ($p < .001$) (Table 1).

TABLE 1. Characteristics of Vietnam Era Twin Registry Twins by Rheumatoid Arthritis Diagnosis

Characteristics	Rheumatoid Arthritis				p^b
	Yes[a]		No[a]		
Total, *n* (%)	119	(1.9)[c]	6167	(98.1)	—
Zygosity, *n* (%)					.570
DZ	43	(36.1)	2403	(39.0)	
MZ	76	(63.9)	3764	(61.0)	
Mean age, yrs (SD)	40.6 (2.9)		40.6 (2.9)		.899
Mean BMI (SD)	26.1 (4.0)		26.0 (3.7)		.662
Education, *n* (%)					.015
Less than HS	6	(5.0)	208	(3.4)	
HS grad or GED	43	(36.1)	1876	(30.4)	
Technical school	19	(16.0)	974	(15.8)	
College grad	47	(39.5)	2362	(38.3)	
Graduate school	4	(3.4)	747	(12.1)	
Smoking status in 1987, *n* (%)					.127
Never	30	(25.2)	2037	(30.0)	
Former	36	(30.3)	1870	(30.3)	
Current	53	(44.5)	2260	(36.6)	
Combat exposure, *n* (%)					.009
Did not serve in SEA	68	(57.1)	3790	(61.5)	
Served in SEA, but no combat	6	(5.0)	571	(9.3)	
Low combat	8	(6.7)	649	(10.5)	
Medium combat	20	(16.8)	694	(11.3)	
High combat	17	(14.3)	463	(7.5)	
History of depression, *n* (%)					<.001
Yes	25	(21.0)	422	(6.8)	
No	92	(77.3)	5740	(93.1)	
Mean PTSD symptom score in 1987 (SD)	33.5 (13.5)		25.4 (9.4)		<.001

[a]Percentages may not add up to 100% due to missing data and rounding.
[b]Fisher's exact test to calculate *p* values for categorical variables, *t* test for continuous variables.
[c]95% confidence interval, 1.6–2.3.
DZ = dizygotic; MZ = monozygotic; SD = standard deviation; BMI = body mass index; HS = high school; GED = General Educational Development Test; SEA = Southeast Asia; PTSD = posttraumatic stress disorder.

There is a strong monotonic trend ($p_{trend} = .001$) between the PTSD symptom score and the prevalence of RA (Fig. 1). Twins in the lowest symptom quartile have an RA prevalence of <1% and twins in the highest symptom quartile have a prevalence of closer to 4%. The OR estimates examining the association between PTSD and RA are presented in Table 2. In both the unadjusted and adjusted analysis of all twins, there is a strong significant trend in the association of PTSD with RA ($p_{trend} < .001$). Compared with those in the lowest quartile of PTSD symptom scores, those in the highest quartile are nearly five times more likely to report a physician diagnosis of RA in the unadjusted model (OR, 4.9; 95% CI, 2.7–8.9). Adjustment for potential confounders slightly attenuated the observed increase in prevalence, but those in the highest quartile of PTSD symptoms were nearly four times as likely to have reported RA compared with those in the lowest PTSD symptom quartile (OR, 3.8; 95% CI, 2.1–6.1). The association between PTSD symptoms and RA is still significant in both the unadjusted and adjusted within-pair analysis. However, compared with the unpaired twin analysis, the magnitude of the association is reduced in the within pair analysis, which controls for familial/genetic/shared environmental factors ($p_{trend} = .006$). Nevertheless, these findings persist even when adjusted for confounders and examined within the twin pairs ($p_{trend} = .022$). In addition, a 4-point increase in PTSD symptoms is associated with a 20% increase in the likelihood of RA in both the all-twin adjusted model (OR, 1.2; 95% CI, 1.2–1.3; $p < .001$) and the adjusted, within-pair twin model (OR, 1.2; 95% CI, 1.0–1.3; $p = .022$) (Table 2).

DISCUSSION

Our results add to the limited knowledge about the link between PTSD and adult-onset RA. These data suggest a significant association between having a history of PTSD symptoms and a diagnosis of RA among males in the community. The association between PTSD symptoms and RA is not explained by obvious confounding factors, such as depression, cigarette smoking, combat exposure, or demographics. Finally, the results of the within-pair analysis show that the

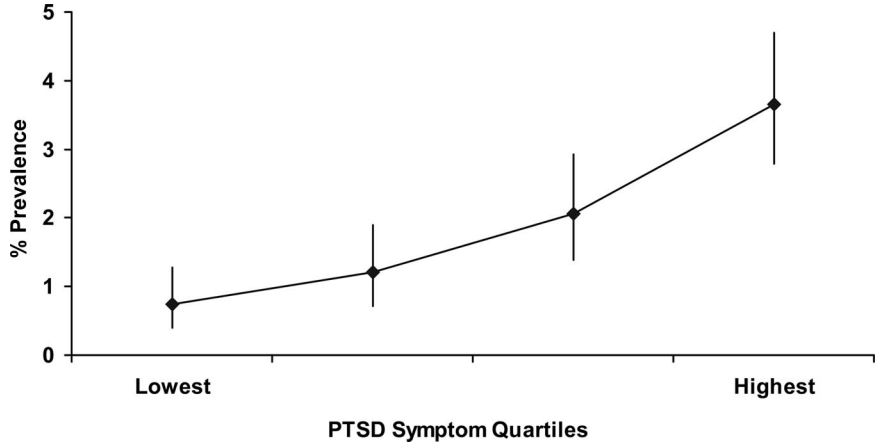

Figure 1. Prevalence of rheumatoid arthritis (%) and 95% confidence intervals by posttraumatic stress disorder (*PTSD*) symptom quartiles.

TABLE 2. Association Between Posttraumatic Stress Disorder (PTSD) Symptoms and Rheumatoid Arthritis for PTSD Quartile and Continuous Score Measures

PTSD	All Twins		Within-Pair Effects	
	OR	95% CI	OR	95% CI
Unadjusted				
Quartile 1	1.0	—	1.0	—
Quartile 2	1.7	(0.8, 3.3)	2.4	(1.0, 6.0)
Quartile 3	2.8	(1.5, 5.3)	2.6	(1.1, 6.2)
Quartile 4	4.9	(2.7, 8.9)	2.3	(1.0, 5.4)
Symptom score[a]	1.3	(1.2, 1.4)	1.2	(1.1, 1.3)
p_{trend} value[a]		<.001		.006
Adjusted[b]				
Quartile 1	1.0	—	1.0	—
Quartile 2	1.5	(0.8, 3.1)	2.6	(1.0, 6.6)
Quartile 3	2.6	(1.4, 5.1)	2.5	(1.0, 5.9)
Quartile 4	3.8	(2.1, 6.1)	2.0	(0.9, 4.7)
Symptom score[a]	1.2	(1.2, 1.3)	1.2	(1.0, 1.3)
p_{trend} value[a]		<.001		.022

[a] Symptom score/linear tread accessed by the continuous PTSD symptom score, in 4-point increments, or the continuous within-pair component in generalized estimating equation linear regression.
[b] Adjusted for age, smoking status, body mass index, combat exposure, education, and depression.
OR = odds ratio; CI = confidence interval.

link between PTSD symptoms and RA is not fully explained by common familial or genetic influences.

Previous studies (3–7) have documented links between PTSD and a number of chronic medical problems. Our results provide additional evidence of a link between PTSD symptoms and adult-onset RA. To our knowledge, only one other study (7) among community-dwelling adults has reported a significant association between PTSD and RA. The latter study (7) was based on a 1986 national survey of male Vietnam veterans, and it also reported a 2% RA prevalence rate, using a multimethod RA assessment, reinforcing the validity of the results reported. Previous studies (6,11,12,31,32) have suggested an association between PTSD and increased proinflammatory activity and related diseases. Nevertheless, it is possible that RA and PTSD share common social and environmental risk factors, which may play a role in their co-occurrence. Although a previous study found a link between RA and PTSD, that study did not adjust for an extensive set of potential confounding factors. In the current study, we controlled for a large number of potential confounding factors that might explain the association between PTSD and RA. For example, we included educational attainment in our models to account for socioeconomic status, which is known to be related to both mental health disorders and greater medical morbidity (33,34). Similarly, we adjusted for cigarette smoking and BMI, which are both associated with PTSD as well as increased medical morbidity (3,5,6,31). In addition, cigarette smoking is a suspected risk factor for RA (16,17,35). We found that the link between PTSD symptoms and RA was not fully explained by any of these common risk factors. However, we did not have all of the potential confounding factors that might explain this relationship. For example, risk factors for RA, such as childhood exposure to common viruses, second-hand smoke, and other environmental factors during childhood, were unavailable. Thus, it is possible that there were other environmental factors associated with RA and PTSD that played a role in this link. Some of these potential factors also include childhood abuse or exposure to adverse life events during childhood, which have been linked with both future health status (36) and PTSD (19,37). However, generally twins are likely to have had similar childhood and adolescent environments (20,21). Thus, the co-twin approach examining the within-pair association between PTSD and RA would have adjusted for a sizable portion of these potential confounders.

Our analysis included level of combat exposure as a covariate. Traumatic exposure is a potential risk factor for many health problems (3,38,39) and is clearly associated with symptoms of PTSD (1,40,41). However, combat did not significantly attenuate the association between PTSD symptoms and RA. We did not have other measures of traumatic exposures, and it is possible that other noncombat trauma is more relevant to the development of RA.

Our within-pair analysis of PTSD symptoms and RA has implications for understanding the etiology of RA. Although we observed a change in the magnitude of the association between PTSD symptoms and RA, when the analysis was restricted to twin pairs and adjusted for relevant confounding factors, this association was still significant. This suggests that neither common familial nor genetic factors completely explain the relationship of PTSD symptoms and adult RA onset. It is possible that traumatic stress, which is associated with alterations in immune functioning and increased inflammation activity (6,11,12,31,32,39), can lead to increased vulnerability to inflammatory-related diseases, including atherosclerosis, ischemic heart disease, and RA (6,7). Future longitudinal population-based studies could help to untangle the pathways linking PTSD and RA. Such studies ideally would include physician diagnoses of RA, as well as physiologic measures confirming the presence of rheumatoid disease (16,35,42,43). Also, further research should include a more detailed set of measures for different trauma exposures and comorbid mental disorders. With respect to the latter, depression is known to be comorbid with PTSD (1). However, as in a previous study (6), we found that depression was not significant in the final model with PTSD also included. Furthermore, adding or removing depression from the model made little difference in our final results.

Further limitations need to be considered when evaluating these reported results. First, we did not have any information on either the severity or the clinical status of the reported RA disease among the twins. RA is a variable condition with mild, moderate, and severe disease, as well as stable versus rapid

disease progression, which can only be formally diagnosed using clinical observation and laboratory data (16,35,42,43). In addition, our measurement of PTSD symptoms in 1987 was based on an earlier conceptualization of this syndrome and, therefore, has limitations (5,6,26). It would be desirable to replicate our findings, using information on RA clinical status, a more current measure of PTSD based on *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* criteria, and a longitudinal research design. Second, our analysis only included males; therefore, the results cannot be generalized to women. Third, there is a possibility of a bias because individuals with greater PTSD symptoms may seek medical care more frequently than those with fewer symptoms (3). In addition, it is conceivable that individuals suffering from PTSD may be more likely than those without PTSD to overreport physical illnesses (3), contributing to the observed association. To date, however, a number of independent studies have shown a link between self-reported PTSD symptoms and medical morbidity and mortality, using physiologic measurements and/or death certificate data (5,6,44–46). This increases confidence that our results are unlikely entirely due to self-report bias. Fourth, our study response rate was lower than optimal, and this could have biased our study results. Finally, because our data are primarily cross-sectional, we could not fully examine the temporal relationship between PTSD symptoms and RA.

In conclusion, our findings provide evidence of a link between PTSD and RA onset among adult males. This finding is not explained by shared familial or genetic risk factors. Rheumatoid disease and PTSD are debilitating and costly conditions both for the individual and society (1,16,35,38,47,48). Recent research has suggested that after exposure to the World Trade Center attacks in New York City, adult workers who received brief mental health counseling at the worksite had improved health outcomes up to 2 years after this event (49). If these findings are replicated among other populations, then the burden of medical morbidity associated with PTSD might be reduced in the future through such interventions. Efforts to understand the association of PTSD with RA may prove useful in identifying modifiable risk factors contributing to RA and in developing more effective intervention strategies, including early treatments for those exposed to such traumatic events.

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