Perceived stress and inflammatory arthritis: a prospective investigation in the Studies of the Etiologies of Rheumatoid Arthritis (SERA) cohort

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Abstract

Objective: The aim of this study was to determine the association of perceived stress with incident inflammatory arthritis (IA) defined as having at least 1 joint consistent with rheumatoid arthritis (RA)-like synovitis based on exam.

Methods: We conducted a prospective cohort study in the Studies of the Etiologies of Rheumatoid Arthritis (SERA). Participants without IA were recruited if they were a first degree relative of a RA proband or screened positive for anti-cyclic citrullinated peptide autoantibody (ACPA). Perceived stress was measured using the Perceived Stress Scale-14 (PSS) in which scores can range from 0 to 56 and a higher score indicates greater perceived stress. The total PSS score as well as two sub-scores indicative of perceived distress and self-efficacy were averaged across all study visits until development of IA or last follow-up. Hazard ratios (HRs) and 95% confidence intervals (CIs) of IA associated with average PSS scores were obtained using Cox proportional hazards models.

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Results: The mean total PSS score was 20.4. We found that a one-point increase in the perceived distress score was significantly associated with a 10 percent increase in the risk of IA (adjusted HR: 1.10; 95%CI: 1.02, 1.19). Total PSS and self-efficacy were not associated with IA risk (adjusted HR: 1.05 (95%CI: 0.99, 1.10) and 1.04 (95%CI: 0.91, 1.18), respectively.

Conclusions: An association between perceived distress and incident IA was observed in this at-risk cohort. Replication of this finding in other preclinical and at-risk RA populations is needed.

Introduction

The relationship between high levels of psychological stress and increased disease activity in those with rheumatoid arthritis (RA) has been established (1–6). However, the contribution of psychological stress to the risk of developing future RA remains unclear. Proposed mechanisms of how stress may affect risk of progression to RA include dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis or through promotion of unhealthy behaviors such as smoking, a known RA risk factor (7–9).

Previous studies examining associations between psychological stress and RA onset have used a variety of measures of stress, including assessing post-traumatic stress disorder (PTSD) symptoms and stressful life events (e.g. divorce, being fired from a job, and experiencing the death of a family member). A retrospective cohort study of U.S. veterans who were deployed to the wars in Afghanistan and Iraq found a positive association between ICD-9 codes for PTSD and RA onset (10). Similarly, the Nurses' Health Study II reported a positive association between self-reported PTSD symptoms identified from a Brief Trauma Questionnaire and risk of RA diagnosis (11). Mixed findings have been reported for the association between retrospective measures of stressful life events and RA onset. In a case-control study, stressful life events were assessed by the Social Readjustment Rating Scale during the year before RA or osteoarthritis onset in cases and controls, respectively (12). This retrospective study found that those who developed RA were more likely to have stressful life events in the year prior to onset compared to controls. In contrast, a matched case-control study found no associations between the occurrence of stressful life events and RA (13). The infrequency of stressful life events is a limitation, particularly during a single year as assessed on the Social Readjustment Rating Scale. Furthermore, the way in which individuals perceive or cope with traumatic and stressful events may vary person to person. A more general measure of psychological stress is perceived stress, which is the degree to which individuals identify life experiences as unpredictable, uncontrollable or generally overwhelming (14). A recent study in a clinically suspect arthralgia population that was identified in a clinical setting, did not observe differences in baseline perceived stress levels between those who did and did not go on to develop clinical arthritis within two years (15). However, the association between perceived stress and the risk of developing RA is unknown in a non-clinic population.

The aim of this current study was to determine the association of perceived stress with incident inflammatory arthritis (IA) defined as at least 1 joint consistent with RA-like synovitis. We hypothesized that higher perceived stress would be associated with an increased risk of subsequently developing IA. This study was conducted using data from

participants in the ongoing Studies of the Etiologies of Rheumatoid Arthritis (SERA) prospective cohort (16, 17). This longitudinal cohort consists of an at-risk population of individuals who are followed for the development of IA and RA. Our study expands on the previous literature by using the Perceived Stress Scale (PSS) (14) as a general measure of psychological stress, rather than assessing stressful life events, in a population at risk for the future development of RA.

Patients and Methods

We conducted a prospective, longitudinal cohort study using data from the ongoing SERA multisite cohort that was established in 2002 (16, 17). SERA (n=2037 participants) populations at increased risk of developing future RA included in this study are: 1) first-degree relatives (FDRs) of RA probands who may be at elevated genetic and shared environmental risk (FDR Cohort), and 2) individuals who screened positive for the presence of anti-citrullinated protein antibodies (ACPAs) at community-based health fairs in Colorado (Health Fair Cohort).

SERA participants that are positive for any RA-related autoantibody are invited to attend annual study follow-up visits, otherwise follow-up visits take place every two years (17). At each study visit, a board certified rheumatologist conducted a 66/68-count joint examination. Participants with one or more swollen joints consistent with RA-like synovitis were determined to have IA, the primary outcome of interest. When a participant presents with the signs of IA, they can be further classified as having RA if they meet the 2010 ACR/ European League Against Rheumatism (EULAR) criteria (18). Because the primary outcome of this study is IA, even if a subset meets the RA classification criteria, we still refer to these participants as incident IA cases. Blood samples were taken at each visit to measure rheumatoid factor (RF) by nephelometry (Dade Behring, Newark, DE, USA), anti-CCP antibodies (CCP2, CCP3 and CCP3.1; Inova Diagnostics, Inc.), and C-reactive protein (CRP). For this study, autoantibody status at baseline was defined by the presence of any RF or anti-CCP antibody. Subjects were also genotyped for the presence of shared epitope (SE) HLA-DR4 and HLA-DR1 alleles via a real-time PCR approach and were considered positive if one or more alleles contained the SE (17). Questionnaires were administered at each visit capturing sociodemographic characteristics and relevant exposures including: age, sex (male or female), race (non-Hispanic white or other), education (high school or > high school), household income ($40,000 or >$40,000), smoking status (ever or never).

The primary exposure of interest was perceived stress as measured by the PSS-14 at each study visit prior to the development of IA. The PSS is a 14-item questionnaire assessing the degree to which life situations over the past month were uncontrollable or overwhelming (14) and is described further below. Because the PSS-14 was first administered in the SERA cohort beginning in 2007 (rather than 2002), we considered the first visit in which the participant completed the PSS-14 as the "baseline visit." Subsequently, participants were included in the current study if they were free of IA/RA at this baseline visit and were followed for the development of IA or RA between 2007 and 2018 (n=448). Participants attended 2 visits on average (SD: 0.4) and had an average of 4 years of follow-up (SD: 2.5) over 1,451 visits (1876.9 person-years of follow-up).

The PSS-14 consists of 14 items in which the responses were rated on a five-point Likert scale from 0 (never) to 4 (very often). Seven items on the PSS-14 are negatively worded (items 1, 2, 3, 8, 11, 12 and 14) and the seven other items are positively worded (items 4, 5, 6, 7, 9, 10 and 13) (Supplemental Table 1). First, we calculated the total PSS-14 score at each study visit by summing all items after reversing the score of the positively worded items for a score ranging from 0 to 56. The total PSS-14 score is a measure of perceived stress and a higher score corresponds to higher perceived stress. Supplemental Table 1 provides the 14 items on the PSS-14, distinguishes between the positively and negatively worded items, and further describes the reverse scoring process. Second, we calculated two sub-scores by summing the negatively and positively worded items separately, with maximum sub-scores of 28. The negatively and positively worded item sub-scores are considered to reflect the constructs of perceived distress and self-efficacy, respectively (19, 20). Hereafter, the two sub-scores when referenced individually will be referred to by their respective constructs. Lastly, the total PSS-14 score as well as the two sub-scores were averaged across all study visits until the development IA (i.e. not including study visits after the participant was determined to have IA) to be analyzed as continuous variables in the Cox proportional hazards models described below.

For descriptive purposes (i.e., in Table 1), we categorized the total PSS score as low perceived stress (bottom 20%, PSS-14 score 13), moderate perceived stress (PSS-14 score of 14–26), and high perceived stress (top 20%, PSS-14 score 27) using percentiles that have been used previously (21, 22). Additionally, for comparison with the general US population (23) and a clinically suspect arthralgia population (15), we calculated a PSS-10 score based on the PSS-14 questionnaire.

Statistical Analysis

Associations between categories of the perceived stress scores from all visits and sample characteristics were assessed using chi-square tests for categorical characteristics and ANOVA for continuous characteristics. Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident IA associated with continuous PSS-14 scores prior to the development of IA were obtained using Cox proportional hazards models. Years of follow-up served as the time scale and were calculated starting from the baseline visit to either the final study visit or incidence of IA. The following baseline covariates were included in the adjusted model: education, smoking status (ever smoker), autoantibody status, and cohort (i.e. FDR cohort or Health Fair cohort) based on univariate associations (p-values <0.2) with IA status. Smoking and autoantibody status were included as precision variables as they were associated with IA but not with PSS. Due to non-significant bivariate associations of age, gender and race/ethnicity with IA status, these variables did not meet the conditions for confounding and thus were not included in the final models. The proportional hazard assumption was satisfied based on the cumulative sums of residuals using the 'assess ph' option in PROC PHREG (24). All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results:

Study population characteristics by perceived stress categories prior to the development of IA are presented in Table 1. Younger participants were more likely to have higher perceived stress (PSS-14 score 27) than older participants. Additionally, non-Hispanic white participants or those with higher household incomes were more likely to have lower perceived stress (PSS-14 scores 13). There were no significant differences in perceived stress by autoantibody or C-reactive protein status. In the overall analytic sample, the average PSS-14 score across all visits prior to the development of IA was 20.4 (SD: 6.7). During follow-up, 31 incident cases of IA developed. The average PSS-14 score was 20.2 (SD 6.7) in those who did not develop IA and 22.4 (SD 7.1) in those who transitioned to IA during the study.

In the unadjusted Cox proportional hazard models, a one-point increase in the total PSS score and the perceived distress score were significantly associated with a 6% and 10% increase in the risk of incident IA, respectively (Table 2). After adjustment for baseline autoantibody status, education, ever smoking status and cohort the perceived distress score remained significantly associated with incident IA (HR: 1.10; 95% CI: 1.02, 1.19). The adjusted models for the total PSS score or the self-efficacy score had the same trend but did not reach statistical significance (Total PSS score HR: 1.05; 95% CI: 0.99, 1.10. Self-efficacy score HR: 1.04; 95% CI: 0.91, 1.18).

Discussion:

In a cohort of individuals at-risk of developing IA, we found that participants with higher perceived distress were at an increased risk of developing IA. We did not find an association between IA and total perceived stress or self-efficacy. A potential explanation for the observed association between perceived distress and incident IA may be due to the underlying constructs in the PSS sub-scores (i.e. perceived distress vs. self-efficacy) (19, 20). Our results suggest that IA risk is associated with perceived distress, a subjective stressor defined as how an individual may appraise an objective stressor (e.g. loss of a job), rather than internal self-perceptions such as self-efficacy (25).

In this at-risk population the average total PSS-14 score was 20.4. In order to compare our score with other studies we evaluated total perceived stress on the PSS-10 scale, and found that the average score was comparable to other populations. In this study, the average total PSS-10 score for the overall sample was 14.0 (SD: 6.4), and the score for age groups 25–34 and 55–64 were 16.7 (SD: 6.1) and 13.9 (SD: 6.6), respectively. In comparison, a clinically suspect arthralgia population had a mean PSS-10 score of 13.5 (SD: 7.6) (15). For reference, the PSS-10 scores are 17.5 (SD: 7.3) and 14.5 (SD: 7.2) for individuals aged 25–34 and 55–64, respectively, in the general US population (23). Supplemental Table 1 identifies the 10 items from the PSS-14 that were used to determine the PSS-10 score.

Studies in RA patient populations have reported on the effectiveness of cognitive behavioral therapy (CBT) – particularly directed toward mindfulness or stress-management interventions – on pain, disease activity and stress reactivity (26–31). However, a recent

meta-analysis exclusively focused on mindfulness interventions in RA patients determined that the current state of evidence is promising, but limited by the sparse number of randomized trials that have been conducted (31). Of note, studies conducted in RA (28) and fibromyalgia populations (32) suggest that those with elevated psychological distress may receive the greatest benefit from CBT stress management. RA patients have also shown a willingness to discuss their mental health when the rheumatologist initiates the conversation (33). Thus raising the necessitiy of being able to identify patients who may benefit from behavioral interventions and integrating effective interventions targeting psychosocial factors like perceived distress in a clinical setting. As an example, physican-led problem solving therapy, a type of CBT, may be practical in preclinical RA populations as a recent meta-analysis suggested its effectiveness in a primary care setting (34). Therefore, interventions based on cognitive behavioral principals may be effective in the preclinical period, particularly in individuals with increased perceived distress.

Future research on the biologic mechanisms of stress increasing incident RA risk is needed. This research may focus on components of the immune/inflammatory system and/or HPA axis, and the potential role of chronic inflammation as a link between stress and preclinical RA. Elevated levels of pro-inflammatory cytokines, such as interleukin (IL)-6, are important markers of systemic inflammation in preclinical RA populations (35, 36). Coincidently, cytokines are also elevated in a state of chronic stress as it prolongs HPA axis activation and the inflammatory response (37). HPA axis dysregulation as characterized in PTSD is thought to increase systemic inflammation as a potential mechanism behind the increased risk of incident RA in patients with PTSD (11). Furthermore, elevated pro-inflammatory cytokine concentrations were found in RA patients with comorbid PTSD compared to those without PTSD, suggesting an elevated inflammatory response (38). Stress management training among RA patients in a randomized study – who in general have higher levels of cytokines (2, 39) and salivary cortisol (40) – resulted in lower levels of IL-8 (41) and cortisol (42), highlighting the links between stress, immune and inflammatory components. Nevertheless, bidirectional links between perceived stress, inflammation and RA development should be considered. For example, chronic exposure to inflammatory cytokines, which are elevated in preclinical RA, may lead to depressive symptoms (43).

In addition to the studies linking stress to inflammatory components, other studies have examined similar relationships with anxiety and depression, which are both associated with stress levels (44). A recent study showed an increase in the incidence of anxiety disorder prior to the diagnosis of RA and the authors suggested that mood disorders could potentially be early symptoms of immune-mediated inflammatory diseases like RA in some patients (45). Similar findings were observed in another cohort, in which study participants with depression were at an increased risk of developing RA (46). Inflammation and depression have been linked through studies observing elevated cytokine and CRP concentrations in depressed patient populations compared to nondepressed populations, and improved depression symptoms in response to anti-inflammatory COX-2 inhibitor therapy (47). In established RA populations, depression symptoms have been associated with increased IL-10 in sera (48) and poor response to anti-TNF therapy (49). Altogether, these studies suggest that inflammation may be the underlying mechanism between the development of

IA and stress, and that cortisol and cytokines may be useful biomarkers in preclinical populations.

In conclusion, we found an association between perceived distress and incident IA. The generalizability of our results is limited to at-risk populations that are positive for RA-related autoantibodies or may have genetic risk due to family history. While these results require replication in other populations, our finding suggests that the incorporation of stress management or mindfulness activities based on cognitive behavioral principals may be beneficial for individuals at-risk of developing IA, particularly among those with higher perceived distress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding support:

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Significance and Innovations:

- This study expands upon the previous literature examining associations between psychological stress and inflammatory arthritis/rheumatoid arthritis onset. We assessed the risk of developing future inflammatory arthritis by using a general measure of psychological stress, rather than assessing stressful life events or PTSD symptoms, in a non-clinical, at-risk population.

- Perceived distress is significantly associated with incident inflammatory arthritis in a prospective cohort of at-risk individuals.

Table 1.

Baseline sample characteristics overall and by averaged perceived stress scores across all pre-IA visits, SERA (N=448)

Characteristic	Overall	Low perceived stress (13) N=91	Moderate perceived stress (14–26) N=259	High perceived stress (27) N=98	p-value
Age, yrs., mean (SD)	49.5 (14.3)	55.9 (15.1)	48.9 (13.9)	45.2 (12.4)	<.0001
Sex, Female	329 (73.4)	62 (68.1)	186 (71.8)	81 (82.6)	0.05
Race, NHW	366 (81.7)	84 (92.3)	213 (82.2)	69 (70.4)	0.0005
Income, >$40k	326 (77.8)	71 (80.7)	194 (80.8)	61 (67.0)	0.02
Education, >HS	372 (83.4)	80 (87.9)	213 (82.9)	79 (80.6)	0.38
Smoking status, ever	171 (39.2)	40 (43.9)	95 (36.7)	36 (36.7)	0.44
Shared Epitope, positive	249 (55.7)	52 (57.1)	139 (53.8)	58 (59.2)	0.63
Autoantibody status, positive	106 (23.7)	26 (28.9)	58 (22.4)	22 (22.4)	0.43
C-reactive protein, positive (3mg/L)	126 (29.4)	18 (21.2)	75 (30.2)	33 (34.4)	0.13
Body Mass Index, kg/m^2, mean (SD)	27.8 (6.7)	27.2 (6.2)	28.1 (7.1)	27.7 (6.3)	0.60

Notes. All values n(%) unless otherwise stated. Chi-square p-values presented for categorical variables and overall F-test p-values presented for continuous variables. Missing values: shared epitope (n=1), education (n=2), income (n=29), C-reactive protein (n=19), body mass index (n=9)

Table 2.

HRs for the association of PSS with incident IA (N=31 events)

	Unadjusted HRs (95% CI)	Adjusted HRs (95 %CI)[*]
PSS total score	1.06 (1.00, 1.12)	1.05 (0.99, 1.10)
Perceived Distress	1.10 (1.00, 1.20)	1.10 (1.02, 1.19)
Self-efficacy	1.09 (0.98, 1.21)	1.04 (0.91, 1.18)

[*] Adjusted for cohort, baseline autoantibody status, education, and ever smoking status