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Posttraumatic Stress Disorder and Risk for Incident Rheumatoid Arthritis

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Abstract

Objective—To examine the association between symptoms of post-traumatic stress disorder (PTSD) and rheumatoid arthritis (RA) risk in a prospective cohort and to characterize the role of smoking in this relationship.

Methods—A subset (N = 54,224) of the Nurses' Health Study II, a prospective cohort of female nurses, completed the Brief Trauma Questionnaire and a screen for PTSD symptoms. Participants were categorized based on trauma exposure and number of PTSD symptoms. Incident RA cases (N = 239) from 1989 to 2011 were identified. Cox proportional hazards models were used to calculate hazard ratios (HRs) and confidence intervals (CIs) between PTSD symptoms and incident RA. To identify the impact of smoking, secondary and subgroup analyses were performed. In all analyses, PTSD and smoking were lagged two years before the development of RA.

Results—Compared to no history of trauma/PTSD symptoms, the HR for ≥4 PTSD symptoms and incident RA was 1.76 (95% CI 1.16, 2.67) in models adjusted for age, race and socioeconomic status. The risk for RA increased with increasing number of PTSD symptoms (P = 0.01). When smoking was added to the model, the HR for RA remained elevated (HR 1.60; 95% CI 1.05, 2.43). In a subgroup analysis, excluding women who smoked before PTSD onset, results were unchanged (HR 1.68; 95% CI 1.04, 2.70).

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Conclusion—This study suggests that women with high PTSD symptomatology have an elevated risk for RA, independent of smoking, adding to emerging evidence that stress is an important determinant of physical health.

Post-traumatic stress disorder (PTSD) is a mental disorder that may develop after exposure to a traumatic event (1). PTSD is characterized by intrusive memories of the event, increased arousal, avoidance of experiences associated with the traumatic event, and loss of interest in activities and relationships (2). In the U.S., estimates of the lifetime prevalence of PTSD range from 4.0% to 8.7% (3). In addition to adverse effects on mental health, PTSD appears to increase the risk of a number of chronic diseases, including diabetes and cardiovascular disease (4–6).

The role of PTSD in the risk for autoimmune diseases has garnered particular interest because several studies implicate stress in the pathogenesis of autoimmune diseases such as ankylosing spondylitis (7), psoriasis and hypothyroidism (8). For example, studies have shown that work stress may be a risk factor for ankylosing spondyloarthritis (9), and stressful events are associated with ankylosing spondyloarthritis disease activity measures (10).

The mechanism of this association may be through dysregulation of the HPA-axis response, leading to heightened systemic inflammation (11, 12), as occurs in rheumatoid arthritis (RA). Two studies have found associations between PTSD and prevalent RA among male Vietnam War veterans (8, 13). Another study of U.S. veterans reported an association between PTSD and patient-reported measures of RA disease activity (14). However, these studies had limited generalizability because they were comprised only or predominately of men, and they did not separately examine the risk of RA in patients seropositive for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP) vs. seronegative patients. Analyses stratified by serostatus are important because several studies have suggested that risk factors for seropositive vs. seronegative RA differ (15, 16).

PTSD is associated not only with HPA-axis dysregulation but also with unhealthy behaviors (17, 18), which may be both causes and effects of PTSD. For example, a prospective study reported that smoking predicts the development of PTSD symptoms among rescue workers (19). In addition, several studies have shown that individuals with PTSD are at higher risk for smoking (20–24), and smoking is associated with the development of RA (25). Compared to never smokers, both current and former smokers have a higher risk of RA (26), and risk of RA increases with greater smoking intensity and longer duration of smoking (27). Taken together, these observations suggest that smoking has the potential to be both a confounder and a mediator of the association between PTSD and chronic illnesses. Although smoking has been included as a covariate in previous analyses (8, 13, 28), these studies did not assess the impact of smoking on the relationship between PTSD and RA risk, nor did they include data on smoking at multiple time points during follow-up.

The primary objective of the present study is to examine the association between PTSD and subsequent RA risk in an ongoing observational study of women. The secondary objective is to identify the role of smoking as a confounder and/or mediator of the relationship between

PTSD and RA risk. We address the issues of confounding and mediation using two methods. First, we examine the role of smoking as a confounder of the association between PTSD and risk for RA by adjusting for smoking in multivariable analyses. Second, we examine the role of smoking as a mediator by performing a subgroup analysis, excluding women who smoked before PTSD onset, thereby isolating the effects of smoking as a mediator of the relationship between PTSD and RA. We hypothesize that: 1) PTSD is associated with an increased risk of RA, and 2) smoking both confounds and mediates the association between PTSD and RA risk.

PATIENTS AND METHODS

Study population

NHSII is an ongoing cohort of 116,430 female nurses, ages 25–42 years at enrollment in 1989. Women in NHSII completed questionnaires about lifestyle, health practices and health conditions at baseline and every two years. In 2008, a subset (N = 60,894) who responded to the most recent biennial NHSII questionnaire was asked to participate in a supplemental study, which included the Brief Trauma Questionnaire and a PTSD screener to identify whether and when trauma and PTSD symptoms may have occurred (29). The response rate was 89.2% (N = 54,224). Among women with a diagnosis of RA prior to 2008, the response rate was 92.7%. Participants with self-reported RA/systemic lupus erythematosus (SLE) at baseline in 1989 were excluded (N = 676). Women who did not respond to questions about PTSD were also excluded (N = 3,855), yielding a final study population of 49,693 nurses. The study was approved by the Partners Institutional Review Board. Detailed information about NHSII can be found in previous publications (29).

Identification of RA

Every two years, participants were asked to report if they had received a physician diagnosis of RA. Self-reported cases were confirmed using a two-step process. First, participants were mailed the Connective Tissue Disease Screening Questionnaire (CSQ) (30). Second, medical records were obtained from participants who screened positive for RA or another connective tissue disease on the CSQ. Two board-certified rheumatologists independently abstracted the medical records for components of the American College of Rheumatology (ACR) classification criteria for RA (31). As required by the ACR criteria, participants had to meet at least four of seven criteria to be considered a definite case of RA. In addition, both reviewers had to agree on the diagnosis. These criteria have been used in multiple prior studies to identify cases of RA in the NHS cohorts (32, 33). Participants with RA were further classified as: 1) seropositive if either RF or anti-CCP levels were above the upper limit of normal, or 2) seronegative if neither RF nor anti-CCP was elevated.

Identification of PTSD symptoms

Trauma exposure was identified using the Brief Trauma Questionnaire, a self-report questionnaire derived from the Brief Trauma Interview (34, 35), administered in 2008. This questionnaire assesses traumatic events, such as motor vehicle accidents, natural disasters, physical assault and sexual assault (29). Participants were asked to identify the worst traumatic event and report whether they experienced PTSD symptoms in relation to that

event (36). The date of onset of PTSD symptoms was defined according to the date of worst trauma (37). We used a specially designed question sequence demonstrated experimentally by Kessler and colleagues to improve accuracy of age-of-onset reporting for psychiatric disorders compared to conventional methods (37). Reliability of self-reported age-of-onset of PTSD was assessed by comparing age at first symptoms reported on the questionnaire with age of first symptoms reported in the structured diagnostic interview. The ICC was 0.95, indicating participants reliably reported age-of-onset.

The number of PTSD symptoms was assessed using Breslau et al.'s 7-item screening scale for DSM-IV PTSD (38, 39). Because prior work suggests a dose dependent relationship between number of PTSD symptoms and risk for chronic illness (40), participants were categorized into four groups: 1) no trauma, 2) trauma but no PTSD symptoms, 3) trauma and 1-3 PTSD symptoms, 4) trauma and ≥4 PTSD symptoms. In a previous study, the identification of trauma and ≥4 PTSD symptoms classified PTSD cases with a sensitivity of 85%, specificity of 93%, positive predictive value of 68% and negative predictive value of 98% (38). Among the group of women with ≥4 PTSD symptoms, the median age of PTSD onset was 18.0 years, with a range of 0-43.0 years. This is consistent with studies reporting that trauma exposure often occurs early (41) and symptoms are long-lasting (42), though few studies have examined the impact of trauma occurring before one year of age (43).

Smoking and other covariates

Smoking status was initially reported on the 1989 questionnaire, when subjects were asked whether they were current smokers, whether they had smoked in the past and, if so, the age at which they began to smoke. Current smokers also provided data on average daily cigarette consumption, and former smokers provided data on average daily cigarette consumption prior to stopping. After 1989, smoking status was updated biennially. These data were used to calculate lifetime cumulative pack-years of smoking, which was included in models as a time-varying continuous variable. Additional covariates included: race (Caucasian, not Caucasian) and parental education (≤high school education or > high school education) as a proxy for childhood socioeconomic status.

Statistical analysis

We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between PTSD categories (no trauma, trauma but no PTSD symptoms, trauma and 1-3 PTSD symptoms, trauma and ≥4 PTSD symptoms) and risk for RA. The main model was adjusted for age, questionnaire-year, race and parental education. Sensitivity analyses were performed separately for seropositive and seronegative RA. Based on an *a priori* hypothesis, the effect of smoking on confounding the association between PTSD and RA risk was evaluated by including smoking as a time-varying covariate in the multivariable model. Lifetime cumulative pack years from one wave (two years) prior to ascertainment of case status were used to predict RA. We considered a >10% change in the HR as a potentially meaningful influence of smoking on the association between PTSD and RA (44, 45). To assess whether smoking after the onset of PTSD mediated the increase in RA risk, we also examined the association between PTSD and RA in a subgroup analysis excluding women who started smoking before PTSD onset. A separate subgroup analysis

was performed among women who had never smoked. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Clinical characteristics

Demographic characteristics across trauma/PTSD levels are described in Table 1. Women with the highest level of PTSD symptoms reported more pack-years of smoking than women with no history of trauma and PTSD symptoms. The prevalence of current smoking was 8.0% among women with ≥4 PTSD symptoms compared to 5.6% among women with < 4 PTSD symptoms ($P < 0.0001$). Compared to women with < 4 PTSD symptoms, women with ≥4 PTSD symptoms were also more likely to report > 10 pack years of smoking (22.1% vs. 16.1%; $P < 0.0001$).

PTSD and risk for RA

In a Cox proportional hazards model adjusted for age, questionnaire year, race and parental education, women with ≥4 PTSD symptoms had a 76% increased risk for developing RA (HR 1.76, 95% CI 1.16, 2.67), compared with women with no history of trauma and PTSD symptoms (Table 2). Similar results were observed for the risks of seropositive RA (HR 1.68, 95% CI 1.01, 2.79) and seronegative RA (HR 1.97, 95% CI 0.93, 4.17). However, the results for seronegative RA did not reach statistical significance.

We observed a dose-response relationship, whereby risk of RA increased as the number of PTSD symptoms increased (trauma but no PTSD symptoms: HR 1.25, 1–3 PTSD symptoms: HR 1.31, ≥ 4 PTSD symptoms: HR1.76; *P,trend* = 0.01). Similar dose response relationships were observed in the subgroup of patients with seropositive RA (trauma but not PTSD symptoms: HR 1.16, 1–3 PTSD symptoms: HR 1.13, ≥4 PTSD symptoms: HR 1.68; *P, trend* = 0.05), as well as the subgroup of patients with seronegative RA (trauma but no PTSD symptoms: HR 1.47, 1–3 PTSD symptoms: HR 1.74, ≥4 PTSD symptoms: HR1.97; *P, trend* = 0.10).

Smoking as a confounder

Women with prevalent RA in 2008 were significantly more likely to report > 10 pack years of smoking than women who did not have a diagnosis of RA in 2008 ($P < 0.0001$). However, in analyses examining the association between PTSD symptoms and RA, the HR from the model including smoking status did not differ by 10% from the HR from the model that did not include smoking status (smoking-adjusted HR1.60, 95% CI=1.05, 2.43, p-trend=0.04) (Table 2).

Smoking as a mediator

To assess whether smoking after the onset of PTSD explained elevated RA risk in women with PTSD symptoms, we performed a subgroup analysis excluding women who started smoking before the onset of PTSD (Table 3). When smoking after PTSD onset was included in the multivariable model, the HR for the risk of RA among women with ≥4 PTSD symptoms remained similar (HR 1.68, 95% CI 1.04, 2.70) to the HR using the model that

did not include smoking as a covariate (HR 1.61, 95% CI 1.00, 2.60). In a separate subgroup analysis examining the association between PTSD and RA among women who never smoked, the HR for the risk of RA among women with ≥4 PTSD symptoms was 1.58 (95% CI 0.87, 2.86). The HR for the risk of RA among women with no trauma or trauma and fewer PTSD symptoms was lower (trauma but no PTSD symptoms: HR 1.40;1-3 PTSD symptoms: HR 1.38).

Analysis of potential bias

To ascertain the likelihood of selection bias if women with RA were more likely to drop out of NHSII prior to 2008 and/or less likely to respond to the Brief Trauma Questionnaire, we assessed response rates to the Brief Trauma Questionnaire among women with prevalent RA in 2008 compared to response rates among women in NHSII in 2008 who did not have a diagnosis of RA. Fifty-seven percent of women with RA in 2008 participated in the Brief Trauma Questionnaire, compared to 46.5% of women who did not have a diagnosis of RA. Women with prevalent RA in 2008 did not report significantly higher rates of PTSD symptomatology (defined as ≥4 PTSD symptoms) than women who did not have a diagnosis of RA in 2008 ($P = 0.09$).

DISCUSSION

This study is the first to examine the association between PTSD and RA risk in women, as well as the first to examine the association between PTSD and risk for developing RA in a cohort followed for over 22 years. We found that women with probable PTSD were at increased risk for RA. This association was not substantially altered by the inclusion of smoking in the multivariate model. Similar results were noted in a subgroup analysis excluding women who smoked before the onset of PTSD. These analyses suggest that factors other than smoking need to be considered to understand the increased risk for RA among individuals with a high number of PTSD symptoms.

These data are consistent with two previous studies examining the association between PTSD and risk for RA in male veterans of the Vietnam War. The first study examined the cross-sectional association between PTSD and RA among 2,490 men in the Vietnam Experience Study approximately 17 years after combat exposure (OR=5.2 (95% CI=2.3–11.9) (8). The second study examined 3,134 male twin pairs in the Vietnam Era Twin registry and reported that participants in the highest quartile of PTSD symptoms were 3.8 times more likely to have RA compared to those in the lowest quartile of PTSD symptoms (13). Our study builds upon these studies and supplies much needed data regarding the association between PTSD and risk for developing RA in women exposed to types of trauma common among civilians (28). In addition, our study is the first to examine PTSD symptoms and risk for distinct subtypes of RA, namely, seropositive and seronegative RA since seropositive and seronegative RA may represent two separate pathogenic processes with distinct risk factors (46, 47). In the present study, a similar dose-response relation between PTSD symptoms and increased risk was observed for both RA subtypes.

To characterize the effect of smoking on the association between PTSD and RA risk, we examined smoking as both a confounder and a mediator. A confounder is associated with

both the predictor (PTSD) and the outcome (RA) but is not on the causal pathway between the predictor and the outcome. Classically, confounding is assessed by including the potential confounder as a covariate in multivariable analyses. For this study, we defined, a priori, a confounder as a variable that changes the HR by at least 10%. In our analyses, the addition of smoking decreased the HR for RA risk for women with ≥4 PTSD symptoms by 9.1%. Thus, smoking did not meet the definition for a confounder. Ten percent has been widely used in other studies as the threshold required to classify variables as confounders (44, 45). However, it is an arbitrary cut-off, and it is ultimately up to the reader to determine whether he/she considers this an important change. It is also possible that residual confounding by smoking may exist if participants did not accurately report smoking habits (e.g., due to retrospective reporting before 1989 or inaccurate reporting after 1989), but we believe this is unlikely given previous studies in NHSII, which have used the same smoking variable and noted significant associations with RA (48, 49).

A mediator is associated with both the predictor and the outcome and is also on the causal pathway between the predictor and the outcome. Given that both confounders and mediators are associated with the predictor and the outcome, it may be difficult to separate confounding and mediation via statistical means. In this study, we attempted to isolate the effects of mediation in a subgroup analysis excluding women who started smoking before the onset of PTSD symptoms. Thus, the smoking variable only included information on smoking after PTSD onset. Although this subgroup analysis was not adequately powered, the similarity in the magnitude of the HRs suggests that smoking after the onset of PTSD does not explain the increase in RA risk.

To further isolate the effects of PTSD on RA, independent of smoking, we also examined the association between PTSD and RA among the subgroup of individuals who never smoked. The HR for the risk of RA among women with ≥4 PTSD symptoms was similar to the HR for the risk of RA among women with ≥4 PTSD symptoms in the total study population, adjusted for smoking. There was a suggestion of a dose-response effect, with the HRs for the risk of RA among women with fewer than ≥4 PTSD symptoms being lower than the HR for the risk of RA among with ≥4 PTSD symptoms. However, the number of cases in this subgroup analysis was 130, compared to 239 cases in the total study population. As a result, this subgroup analysis is likely under-powered, and the results were not statistically significant.

This study has several limitations. First, the Brief Trauma Questionnaire was administered in 2008 after many cases of RA were diagnosed. In these cases, data on onset of PTSD symptoms is retrospective to the diagnosis of RA. Hence, although the analysis shows an association between PTSD symptoms and incident RA, we cannot prove causality. We attempted to assess retrospective bias, and found no evidence that women who have RA were more likely to report PTSD/trauma symptoms in 2008. Second, a selection bias may exist because only women who answered the most recent biennial NHSII questionnaire were asked to complete the 2008 Trauma Questionnaire. As a result, a bias may occur if women with RA were less likely to answer questionnaires due to illness and/or disability. However, our analyses showed that women with RA were equally, if not better represented among those sent the Trauma Questionnaire in 2008, compared to those who were not sent the

questionnaire. Third, bias may be introduced if women with high PTSD symptomatology are more likely to seek medical care than women who do not have PTSD. Although studies suggest that individuals with high PTSD symptomatology are more frequent users of mental health services (23), data do not suggest that individuals with high PTSD symptomatology seek medical care more frequently than individuals who have no history of trauma or PTSD symptoms. Future study designs should incorporate methods to identify ascertainment bias that may occur due to higher rates of symptom reporting and/or healthcare seeking among individuals with PTSD.

Our study also has several strengths. Detailed longitudinal follow-up of participants enabled us to incorporate assessments of smoking that may change over time and occur in response to PTSD. In addition, the identification of RA cases was rigorous, involving a validated screening questionnaire, independent medical record review by two board-certified rheumatologists and assessment of the ACR classification criteria for RA. This process minimizes errors in misclassification, which may be significant when participants self-report health conditions such as arthritis (50).

In conclusion, this study suggests that women with high PTSD symptomatology have an elevated risk for RA, independent of smoking. The mechanisms underlying this association are still not well-understood. Further studies are necessary to examine the role of other behaviors and clinical characteristics, such as alcohol consumption and obesity, as potential confounders and/or mediators of the association between PTSD and risk for RA. In addition, assessments of serum and salivary cortisol levels to characterize basal HPA axis activity and the stress response are needed to investigate biologic pathways linking PTSD with an increased risk for RA.

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SIGNIFICANCE AND INNOVATIONS

- Post-traumatic stress disorder (PTSD) is significantly associated with rheumatoid arthritis (RA), with a hazard ratio of 1.76, after adjusting for age, race and socioeconomic status.
- The relationship between PTSD and RA remained the same in analyses examining smoking as a confounder or mediator of the association between PTSD and RA, indicating that this relationship is independent of smoking.

Table 1

Baseline age-standardized characteristics by trauma and PTSD status in the Nurses' Health Study II (N = 49,693)[a]

	PTSD			
	No trauma, no PTSD (n=14,445)	**Trauma, no PTSD (n=25,486)**	**PTSD 1–3 sx (n=4,874)**	**PTSD 4 or more sx (n=4,888)**
Age at study initiation, years, (SD)	34.2 (4.8)	34.9 (4.6)	35.3 (4.5)	35.1 (4.4)
Non-white race/ethnicity,%)	5.7	6.0	5.6	5.6
Parents' education > high school,%)	26.9	28.0	28.4	29.4
Smoking in pack years, mean (SD)	3.0 (6.3)	3.8 (7.2)	4.4 (7.6)	5.0 (8.2)

[a]Values are means (SD) or percentages and are standardized to the age distribution of the study population.

NHSII, Nurses' Health Study II; PTSD, post-traumatic stress disorder; sx, symptoms; SD, standard deviation; BMI, body mass index.

Table 2

Hazard ratios for incident RA, according to self-reported trauma/PTSD categories in NHS II through 2011.

	PTSD and trauma status				
	No trauma, no PTSD symptoms	**Trauma, no PTSD symptoms**	**Trauma, 1–3 PTSD symptoms**	**Trauma, ≥4 PTSD symptoms**	**p for trend[a]**
Risk for RA[b]					
RA cases/person-years	43/253,447	117/526,753	33/132,844	46/135,160	
Age-adjusted HR (95% CI)	1.00 (REF)	1.25 (0.88, 1.78)	1.32 (0.83, 2.07)	1.76 (1.16, 2.67)	0.01
Multivariate-adjusted HR [c] (95% CI)	1.00 (REF)	1.25 (0.88, 1.78)	1.31 (0.83, 2.07)	1.76 (1.16, 2.67)	0.01
Multivariate-adjusted HR + smoking (95% CI)	1.00 (REF)	1.21 (0.85, 1.71)	1.24 (0.78, 1.95)	1.60 (1.05, 2.43)	0.04
Risk for seropositive RA[d,e]					
RA cases/person-years	30/249,376	76/514,666	20/130,229	31/131,401	
Age-adjusted HR (95% CI)	1.00 (REF)	1.16 (0.76, 1.77)	1.14 (0.65, 2.01)	1.69 (1.02, 2.80)	0.04
Multivariate-adjusted HR [c] (95% CI)	1.00 (REF)	1.16 (0.76, 1.77)	1.13 (0.64, 2.00)	1.68 (1.01, 2.79)	0.05
Multivariate-adjusted HR + smoking (95% CI)	1.00 (REF)	1.12 (0.73, 1.71)	1.06 (0.60, 1.87)	1.51 (0.91, 2.51)	0.12
Risk for seronegative RA[e,f]					
RA cases/person-years	13/252,819	41/525,107	13/132,455	15/134,655	
Age-adjusted HR (95%	1.00 (REF)	1.48 (0.79, 2.76)	1.75 (0.81, 3.78)	1.96 (0.93, 4.13)	0.10
Multivariate-adjusted HR [b] (95% CI)	1.00 (REF)	1.47 (0.79, 2.75)	1.74 (0.80, 3.77)	1.97 (0.93, 4.17)	0.10
Multivariate-adjusted HR + smoking (95% CI)	1.00 (REF)	1.45 (0.77, 2.71)	1.69 (0.78, 3.67)	1.85 (0.87, 3.92)	0.14

[a] *P* for trend was calculated based on the median values for each ordinal category

[b] All-RA models: N = 49,693, including 239 cases; total person years = 1,048,205

[c] Cox proportional hazards models, adjusted for age, questionnaire-year, race (Caucasian, non-Caucasian) and parental education (≤high school, > high school)

[d] Seropositive RA models: N = 47,759, including 157 cases; total person years = 1,025,672

[e] Heterogeneity: The p-value from a t-test comparing the models for association between PTSD and risk for seropositive RA vs. seronegative RA was 0.54

[f] Seronegative RA models: N = 49,437, including 82 cases; total person years = 1,045,036 RA, rheumatoid arthritis; PTSD, post-traumatic stress disorder; NHSII, Nurses' Health Study II; HR, hazard ratio; CI, confidence interval

Table 3

Hazard ratios for incident RA through 2011, by trauma/PTSD category, excluding women who smoked before onset of PTSD.[a]

	PTSD and trauma status				
	No trauma, no PTSD symptoms	**Trauma, no PTSD symptoms**	**Trauma, 1-3 PTSD symptoms**	**Trauma, ≥4 PTSD symptoms**	**p for trend[b]**
Risk for RA					
RA cases/person-years	42/252,633	80/383,028	22/97,782	29/98,466	
Multivariate-adjusted HR (95% CI) not including smoking as a covariate[c]	1.00 (REF)	1.23 (0.85, 1.79)	1.26 (0.75, 2.12)	1.61 (1.00, 2.60)	0.07
Multivariate-adjusted HR (95% CI) including smoking as a covariate[d]	1.00 (REF)	1.34 (0.92, 1.96)	1.34 (0.79, 2.25)	1.68 (1.04, 2.70)	0.06

[a] N = 40,168, including 173 cases; total person years = 831,908

[b] *P* for trend was calculated based on the median values for each ordinal category.

[c] Cox proportional hazards models, adjusted for age, questionnaire-year, race (Caucasian, non-Caucasian) and parental education (≤high school, > high school)

[d] Cox proportional hazards models, adjusted for age, questionnaire-year, race (Caucasian, non-Caucasian) and parental education (≤high school, > high school), plus pack years (continuous)

RA, rheumatoid arthritis; PTSD, post-traumatic stress disorder; NHSII, Nurses' Health Study II; HR, hazard ratio; CI, confidence interval.