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Depression and subsequent risk for incident rheumatoid arthritis among women

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Abstract

Objective—We investigated the association of depression with subsequent risk of rheumatoid arthritis (RA) by serologic phenotype.

Methods—We performed a cohort study using pooled data from the Nurses' Health Study (NHS, 1992–2014) and NHSII (1993–2015). Depression was defined using a composite definition: clinician diagnosis, regular antidepressant use, or Mental Health Inventory-5 score <60 by time-updated questionnaires during follow-up. Incident RA cases met research criteria by medical review. Covariates, including smoking, diet, and body mass index, were obtained by questionnaires. Cox regression estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for RA (overall and by serologic phenotype) according to depression status, adjusted for potential confounders. All analyses included a time separation between assessments of depression and the window for RA risk of at least 4 years to lower the possibility that depressive symptoms due to early RA symptoms prior to diagnosis explained any associations.

Results—Among 195,358 women, we identified 858 incident RA cases (65% seropositive) over 3,087,556 person-years (median 17.9 years/participant). Compared to women without depression, those with depression had multivariable HRs (95%CIs) of: 1.28(1.10–1.48) for all RA; 1.12(0.93–1.35) for seropositive RA; and 1.63(1.27–2.09) for seronegative RA. When analyzing components of the composite depression exposure variable, regular antidepressant use was not associated with subsequent seropositive RA (HR 1.21, 95%CI 0.97–1.49) and was associated with seronegative RA (HR 1.75, 95%CI 1.32–2.32).

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Study conception and design. Sparks, Costenbader

Acquisition of data. Sparks, Costenbader

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Conclusion—Indicators of depression, specifically antidepressant use, were associated with subsequent increased risk for seronegative RA, and this finding was not explained by measured lifestyle factors prior to clinical presentation.

Keywords

Depression; Psychosocial factors; Rheumatoid Arthritis; Epidemiology

INTRODUCTION

Rheumatoid arthritis (RA) is a heterogeneous systemic inflammatory disease characterized by a painful polyarthritis with significant impact on quality of life, morbidity, and mortality(1, 2). Seropositive RA (elevated rheumatoid factor [RF] or anti-cyclic citrullinated peptide [anti-CCP]) and seronegative RA have different genetic risk factors(3, 4). While progress has been made in identifying potentially modifiable RA risk factors such as smoking, most of these are specific to seropositive RA(5–7). Among women, post-menopausal status is a strong risk factor for seronegative RA, but not seropositive RA(8). Therefore, seropositive RA and seronegative RA may be different diseases that have similar clinical presentations but different etiologic factors. Few risk factors have been established for seronegative RA.

Patients with depression as well as individuals with depressive symptoms have increased levels of systemic inflammatory markers such as interleukin (IL)-6 and C-reactive protein (CRP) compared to healthy controls, perhaps due to chronic alterations in the hypothalamic-pituitary-adrenal axis(9–14). In longitudinal studies, depression has been associated with future risk of chronic inflammatory diseases, including cardiovascular disease(15), psoriasis(16), psoriatic arthritis(17), inflammatory bowel disease(18, 19), alopecia areata(20), and systemic lupus erythematosus(21). In a randomized trial, individuals assigned to the antidepressant sertraline (a selective serotonin reuptake inhibitor [SSRI]) had significantly lowered serum IL-6 and CRP levels compared to those assigned placebo, demonstrating that treating depression may lower systemic inflammation(22). IL-6 is thought to be an important inflammatory mediator for mood disorders and has also been shown to be elevated prior to RA onset(23, 24). Thus, it is possible that depression may affect future risk of RA, through increased systemic inflammation.

Two previous retrospective cohort studies suggested that depression may increase risk for developing RA(25, 26). However, conclusions were limited due to possible residual confounding from lifestyle factors such as smoking as well as possible reverse causation bias where early RA symptoms may have lowered mood prior to clinical diagnosis. Depression is highly prevalent among patients with chronic pain conditions such as RA(27, 28). Thus, careful study design is needed to ensure that findings implicating depression as a contributor to RA risk are not due to early RA symptoms inducing depression prior to clinical diagnosis. A strategy to reduce this possibility of reverse causation is to introduce a time interval between the assessments of the predictor (i.e., depression) and the outcome (i.e., RA diagnosis)(29).

Therefore, we aimed to investigate depression and risk for incident RA, overall and by serologic status, using two large cohort studies with repeated measures of depression and potential confounders during lengthy follow-up. We hypothesized that depression would be associated with increased subsequent risk of incident RA. We limited the potential for reverse causation bias by separating the depression exposure and RA outcome assessments by at least four years.

METHODS

Study population

We utilized data from two large cohort studies. The Nurses' Health Study (NHS) was established in 1976 and enrolled 121,700 female registered nurses ages 30–55 years; the NHSII began in 1989 and enrolled 116,430 female registered nurses ages 25–42 years. Participants completed questionnaires at baseline and every two years regarding lifestyle, diseases, family history, and medications. Both cohorts have >90% response rates and only 5% of person-time has been lost to follow-up(30). We limited this analysis to women who completed the first questionnaire in which any indicator of depression was asked and did not have prevalent RA or other connective tissue disease (CTD). All participants provided informed consent and the study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health.

Assessments of depression

Following previous work(21), we assessed presence/absence of depression using three measures: (1)self-reported clinician-diagnosed depression, (2)self-reported regular use of an antidepressant, and (3)depressive symptoms using a 5-item screening questionnaire. Participants were asked whether they had new onset of clinician-diagnosed depression as well as the year of diagnosis (NHS: biennially starting in 2000; NHSII: biennially starting in 2001). Participants were asked whether they had regularly taken drugs in an antidepressant class (SSRIs, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors [SNRIs]). Antidepressants were assessed biennially in the NHS starting in 1996 and 2001 in the NHSII. The Mental Health Inventory (MHI)-5 is a subscale of the 36-item Short-Form Health Survey (SF-35) used for quantifying mental health, scored from 0–100, with higher scores indicating better mental health. Previously, a dichotomized MHI-5 score <60 was shown to have a specificity of 80% in detecting moderate/severe depressive symptoms(31). In the NHS, MHI-5 was assessed in 1992, 1996, and 2000; In the NHSII, MHI-5 was assessed in 1993, 1997, and 2001. Therefore, the baseline of the primary analysis was 1992 in the NHS and 1993 in the NHSII, when MHI-5 was first assessed. For secondary analyses, each different baseline was the date of return of questionnaires when each respective depression measure was first assessed. For the clinician-diagnosed depression analysis, baseline was 2000 in the NHS and 2001 in the NHSII. For the regular antidepressant analysis, baseline was 1996 in the NHS and 2001 in the NHSII. For the MHI-5 analysis, baseline was 1992 in the NHS and 1993 in the NHSII.

In the primary analysis, we considered a composite exposure for depression, such that women were considered to have a history of depression at a given study wave if they had

reported clinician-diagnosed depression, regularly using antidepressants, or had an MHI-5 score <60. History of depression exposure was time-updated such that any woman who had one of the three indicators for depressive symptoms was considered exposed. Non-exposed comparators had none of the three indicators for depressive symptoms at the particular follow-up cycle being analyzed. For example, if a woman was not depressed until the 2003 cycle in the NHSII when she first became depressed by clinician-diagnosed depression and regular use of antidepressants, she was classified as not depressed in the analyses for the 1993–2001 cycles, then as depressed from 2003 onward.

In secondary analyses, we separately analyzed each of the three components of the composite depression exposure (self-reported clinician-diagnosed depression, or regular antidepressant use, or MHI-5 score <60).

Identification of incident RA

The primary outcome was all RA, and the secondary outcomes were seropositive RA and seronegative RA. As in previous studies(6, 29), we used a two-stage procedure to identify incident RA. Participants who self-reported RA on the biennial questionnaires were sent the CTD Screening Questionnaire (CSQ)(32). For those who screened positive on the CSQ, medical records were requested and reviewed independently by two rheumatologists to validate RA cases according to the 1987 American College of Rheumatology (ACR) or 2010 ACR/European League Against Rheumatism classification criteria(33, 34). Information on the dates of diagnosis and symptom onset and clinical laboratory results for RF and anti-CCP tests were obtained from medical records. Seropositive RA was defined as positive RF and/or positive anti-CCP, while seronegative RA was defined as negative RF and anti-CCP. For RA cases diagnosed prior to the clinical availability of anti-CCP tests, serostatus was determined solely by RF status. Presence of fibromyalgia among cases was noted based on mention in the medical records.

Covariates

We considered time-updated covariates for inclusion in multivariable models based on previous studies associating them with depression or RA. Demographic variables included age, race, and US region. US Census-tract median household income by zip code was used as a proxy for socioeconomic status (in quartiles). Smoking pack-years was calculated from the reported number of packs of cigarettes smoked per day and number of years of smoking and categorized as never, 1 to 10, >10 to 20, and >20. Body mass index (BMI) was calculated from reported height and weight and categorized as <25, 25–29.9, or ≥30 kg/m^2. Dietary quality was categorized based on quartiles of the cumulative average Alternative Healthy Eating Index, as previously detailed(35). Cumulative average physical activity was calculated using a validated questionnaire(36), and we defined sedentary activity as <3 metabolic equivalent of tasks hours/week(29). Parity/breastfeeding duration was a combined variable, categorized as: nulliparous, parous and 0 to <1 month, parous and 1–11 months, or parous and ≥12 months. Menopause and postmenopausal hormone (PMH) use was categorized as: premenopausal, postmenopausal and never PMH use, or postmenopausal and ever PMH use. As a proxy for health care utilization, women reported whether or not they

had undergone a physical examination in the previous two years. Self-reported pain was measured using the bodily pain subscale of the SF-36, categorized in quartiles.

Statistical analysis

We pooled data from the NHS and NHSII into a single analysis. All analyses were adjusted for cohort. Person-years of follow-up were calculated from the date of return of the baseline questionnaire for each of the different analyses to the date of censoring (the time each subject was removed from the analysis), whichever came first: RA diagnosis (outcome), reported CTD not confirmed as an RA case, loss to follow-up, death, or end of study (June 1, 2014 for the NHS; June 1, 2015 for the NHSII).

We reported the age-adjusted distribution for covariates by absence or presence of depression as of 2000 for the NHS and 2001 for the NHSII, when all three assessments of depression were first simultaneously assessed in each cohort (not as of baseline for the primary analysis). We also reported clinical characteristics of RA cases, stratified by serologic status.

To minimize potential reverse causation, our primary analysis included a time lag of two questionnaire cycles between the exposure/time-updated covariates and risk window for RA. Therefore, the depression exposure was measured at least 4 years prior to the RA diagnosis in the primary analysis. Cox regression models with time-dependent covariates were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for RA, comparing women with vs. without (reference group) depression by the composite exposure variable. Base models were adjusted for age, cohort, questionnaire cycle, and median household income. The next model additionally adjusted for health factors that included parity/breastfeeding, menopausal status/PMH use, and physical examination. The final model was further adjusted for lifestyle: smoking pack-years, BMI, physical activity, and dietary quality. Similar analyses were performed to investigate associations of depression status with the secondary outcomes of seropositive RA and seronegative RA.

We separately investigated the association of each component of the composite depression measure with RA. In these analyses we dichotomized self-reported clinician-diagnosed depression (yes vs. no), regular use of antidepressants (yes vs. no), and MHI-5 score (<60 vs. <60). Each of these secondary analyses were also lagged by two follow-up cycles and used the same multivariable models as in the primary analysis. In the antidepressant models, we also included a model adjusting for bodily pain since those medications may have been used to treat pain. In the MHI-5 models, we also included a model additionally adjusting for regular antidepressant use since treated depression may have affected mood.

We performed several sensitivity analyses to evaluate the robustness of our findings. First, we performed models with different lagging periods than the primary analysis (no lag, 2-year lag, and 6-year lag. Second, we removed RA cases with fibromyalgia from the analysis to evaluate whether these cases may have impacted the results. Third, we performed the analyses with an alternative baseline of 2000 in the NHS and 2001 in the NHSII, when all three depressive measures were first simultaneously measured. Fourth, we investigated a three-level time-updated depression variable (current, past, and no depression). Fifth, we

adjusted covariates only as of baseline since subsequent changes in these variables (such as smoking, obesity, and sedentary activity) may have mediated the relationship between depression and RA.

We tested the proportional hazards assumption by including an interaction term between depression status and follow-up time for RA risk and verifying no statistical interaction. We assessed for the possibility that collinearity of covariates affected multivariable model performance using the variance inflation factor (VIF). We verified that VIF was <5 for all covariates in models. All analyses were performed using SAS version 9.4. Two-sided *P* values less than 0.05 were considered statistically significant.

RESULTS

Study sample characteristics

We analyzed a total of 195,358 women without CTD at baseline and with any depression measure, starting in 1992 in the NHS and 1993 in the NHSII. Table 1 shows the age-standardized characteristics of the 187,886 study participants as of 2000 in the NHS and 2001 in the NHSII; 59,753 (31.8%) were classified as having any indicator of depression. Clinician-diagnosed depression was present in 9.4% of women. Women with depression were younger than those without depression (mean 52.4 vs. 56.1 years). Women with depression were also more likely to have lower median household income and to be smokers than those without depression. Women with depression also had higher BMI (obesity: 28.3% vs. 21.4%), lower dietary quality, and higher prevalence of sedentary physical activity than those without depression.

Follow-up and incident RA cases

We identified a total of 858 incident RA cases during 3,087,556 person-years of follow-up (median 17.9 [interquartile range 14.2, 17.9] years/participant; mean 15.8 [SD 4.6] years/participant) in the primary analysis that included a last 4-year separation between depression assessment and the RA diagnosis. Among the RA cases, 558 (65.0%) were seropositive and 300 (35.0%) were seronegative.

Table 2 shows clinical characteristics of the RA cases, overall and by serologic status. The median time from first symptom to RA diagnosis was 6 months for seropositive RA and 7 months for seronegative RA cases. Nearly all had symmetric hand inflammatory arthritis. A similar proportion of RA cases had radiographic changes or bone erosions (24.9% in seropositive RA vs. 27.7% in seronegative RA). Fibromyalgia was noted for 3.1% of seropositive RA cases and 9.0% of seronegative RA cases.

Depression and incident RA risk with 4-year lag

Results of the primary analysis are shown in Table 3. All results in this table were lagged by 2 questionnaire cycles (at least 4 years). Women with depression had increased risk for all RA compared to women without depression in the model adjusting for age and demographics (HR 1.39, 95%CI 1.20–1.61). When additionally adjusting for health factors such as parity/breastfeeding, menopause/PMH use, and physical examination, this was

attenuated slightly to a HR of 1.34 (95%CI 1.16–1.56). When additionally adjusting for behaviors that included smoking pack-years, BMI, dietary quality, and physical activity, the association was still present (HR 1.28, 95%CI 1.10–1.48).

In analyses for the outcomes by RA serostatus, depression was not associated with incident seropositive RA risk (multivariable HR 1.12, 95%CI 0.93–1.35). However, there was a strong association of depression with incident seronegative RA that was not explained by measured demographics, health factors, or behaviors (multivariable HR 1.63, 95%CI 1.27–2.09).

Depression and incident RA risk with 6-year lag

We performed a sensitivity analysis that included a longer separation between depression and assessments and the RA risk window (shown in Table 4), to protect more stringently against possible reverse causation whereby early RA symptoms may have influenced depression prior to clinical RA diagnosis. These results were similar to those in the primary analysis. Women with depression had a modest increased risk for all RA (multivariable HR 1.30, 95%CI 1.11–1.52). As in the main analyses, depression was not associated with incident seropositive RA (multivariable HR 1.19, 95%CI 0.98–1.45). Depression remained associated with incident seronegative RA (multivariable HR 1.55, 95%CI 1.18–2.02).

Components of the composite depression exposure

Table 5 shows results for analyses of each component of the composite depression exposure with a 4-year lag. Clinician-diagnosed depression was not statistically associated with all RA (multivariable HR 1.24, 95%CI 0.99–1.55), seropositive RA (HR 1.20, 95%CI 0.91–1.58), or seronegative RA (HR 1.32, 95%CI 0.90–1.94). However, regular antidepressant use was associated with each of the RA outcomes. Compared to no regular use of antidepressants, regular use of antidepressants was associated with all RA (HR 1.37, 95%CI 1.16–1.63), adjusted for bodily pain and other potential confounders. Antidepressant use was not associated with seropositive RA (HR 1.21, 95%CI 0.97–1.49) but was associated with increased risk of seronegative RA (HR 1.75, 95%CI 1.32–2.32). There was no association of dichotomized MHI-5 (<60 vs. ≥60) with any RA outcome.

Sensitivity analyses

Table 6 shows the results of the sensitivity analyses (varying the periods of lag, removing RA cases with fibromyalgia, alternative baseline, 3-level time-updated depression variable, and adjustment for covariates only as of baseline. In all analyses, results were similar to the primary analysis. Depression was modestly associated with increased risk of all RA and more strongly associated with increased risk of seronegative RA.

DISCUSSION

In this large nationwide longitudinal study of nearly 200,000 women with up to 22 years of follow-up, we found that indicators of depression (measured as a composite of self-reported clinician-diagnosed depression, regular antidepressant use, or MHI-5 score <60) were associated with increased risk of developing incident RA. Further, the composite measure of

depression was specifically associated with 63% increased risk for seronegative RA compared to women without depression. Of the three components, antidepressant use was mostly strongly associated with RA risk. The association of depression and increased RA risk was not explained by measured factors including smoking pack-years, body mass index, dietary intake, menopausal status, or physical activity. Our is the first study to identify an association of depression with increased seronegative RA risk while accounting for possible reverse causation. These findings suggest that patients with depression or who are using antidepressant medications may be a population susceptible to RA, but our results should be considered as hypothesis-generating. Therefore, it is possible that depression may be a novel risk factor for seronegative RA, but further studies are needed to replicate our findings.

Our findings build on previous studies that also investigated depression and RA risk(37). A Taiwanese study investigated a bidirectional association between depression and RA using a retrospective cohort study design. The investigators constructed a depression cohort free of RA at baseline and compared RA risk to a non-depression control cohort matched on age, sex, and year(25). In that study, depression was significantly associated with increased incident RA risk (HR 1.63, 95%CI 1.41–1.77), adjusted for matching factors, urbanization, income, and comorbidities(25). Since administrative data were analyzed, they relied on billing codes to identify depression and RA. Data on smoking, physical activity, BMI, menopause, and RA serostatus were unavailable. Therefore, it is possible that results may have been limited by unmeasured confounding and they were unable to investigate associations with RA serologic phenotypes. That study also investigated RA and risk for subsequent depression using similar methods. The RA cohort had HR for subsequent risk of developing depression of 1.69 (95%CI 1.51–1.87) compared to the non-RA control cohort(25). This depression risk was particularly increased in the first two years of follow-up (HR 1.98, 1.43–2.15)(25), illustrating possible reverse causation where early RA may induce depression, perhaps even before clinical diagnosis. A recent similar study using Korean administrative data found that RA increased risk for incident depression, but did not detect an association of depression with incident RA risk(38).

Another retrospective cohort study investigated the association between major depressive disorder (MDD) and RA risk using The Health Improvement Network, an electronic database of general practice medical records in the United Kingdom(26). Patients with MDD had HR for incident RA of 1.38 (95%CI 1.31–1.46; median follow-up of 6.7 years) compared to those without MDD, adjusted for age, sex, smoking status (never/past/current), continuous BMI, comorbidity score, and antidepressant use(26). A sensitivity analysis including a 6-month lag attenuated the results (HR 1.28, 95%CI 1.18–1.38)(26). Interestingly, antidepressant use was associated with increased RA risk among the non-MDD cohort (similar to the results of our present study), but was associated with lower RA risk among the MDD cohort, suggesting that treated depression may modify the future risk of RA(26). That study was limited due to possible unmeasured residual confounding/mediating based on smoking intensity/duration, menopausal status, and physical activity as well as lack of data on RA serostatus. While a sensitivity analysis included a 6-month lag, the results were attenuated suggesting that reverse causality may explain some of the results. It is possible that including a longer lag may have explained the significant association. Therefore, our study adds to the literature by including granular data on many prospectively

measured behaviors and health factors, addressing possible reverse causation bias, and the ability to investigate RA risk by serologic phenotypes.

Our study adds to the growing literature implicating a possible connection between mental health and RA risk(39, 40). A previous study using the NHSII found that increasing number of symptoms of post-traumatic stress disorder (PTSD) increased RA risk(41). Among military members, PTSD was associated with 58% increased risk for any incident autoimmune disease, the most common being RA(42). A twin study also suggested that PTSD was significantly associated with increased RA risk(43). A recent study among individuals exposed to the terrorist attack on the World Trade Center suggested that community members with PTSD had increased risk for incident RA(44). A Scandinavian case-control study found a strong association between stressful events occurring within 1 year and RA onset(45). Among a prospective cohort at high RA risk due to being a first-degree relative or having elevated serum anti-CCP, those with higher levels of perceived stress had increased risk of developing incident inflammatory arthritis(46). Ours is the first study to specifically link mental health with seronegative RA risk, a subtype of RA that has few established risk factors. Future studies may investigate how other aspects of mental health may contribute to the pathogenesis of seronegative RA. While there was no statistical association of depression with seropositive RA, the point estimate could suggest a modest effect that our study was unable to detect due to limited power.

Strengths of our study include the large sample size and lengthy follow-up. We had repeated assessments available of multiple depressive measures as well as rich data on potential confounders that were all prospectively collected. It is possible that some of the time-varying updated covariates (such as obesity and dietary quality) could have mediated the relationship between depression and RA. We treated these variables as potential confounders and, as adjusting for mediators may falsely attenuate true relationships, our estimates may be conservative. In the sensitivity analysis adjusting for only baseline covariates, results were similar. We found no evidence that collinearity of covariates affected model performance in analyses. The lagged exposure design reduced the potential for reverse causation bias explaining the results. We had many incident RA cases, which were verified to meet accepted research criteria, as well as data on serologic status that permitted investigation of RA risk by serologic phenotypes. All RA cases met stringent accepted research classification criteria, but misclassification is still possible since we relied on clinical records. However, all cases had detailed medical record review performed by two separate rheumatologists. Women with diseases that may mimic seronegative RA such as psoriatic arthritis, reactive arthritis, and polymyalgia rheumatica were not considered as RA cases by the reviewers even if RA criteria were otherwise met. Therefore, we have high confidence in the phenotype of the outcomes. We find it unlikely that results are explained by possible misclassification of masquerading diseases as seronegative RA.

Our study also has limitations. We used a composite measure of three different depression assessments in our primary analysis. While previous studies in the NHS cohorts have used similar methods, it is possible that women may have been misclassified(18, 21). The prevalence of any indicators of depression in our study (32%) was higher than previous estimates of depression in adult women in the US (prevalence of 10% according to the CDC)

(47), likely due to the composite measure we used and that the MHI-5 captures depressive symptoms at one point in time, rather than a diagnosis of depression. Each component had lower prevalence when considered alone. The MHI-5 component had the highest prevalence so may have misclassified some women compared to the more stringent components. We performed secondary analyses for the components of the primary exposure variable and found that antidepressant use was most strongly related to RA risk. The prevalence of clinician-diagnosed depression in our study (9.4%) was similar to the population estimate (10%)(47). However, clinician-diagnosed depression was not statistically associated with RA, but had a similar effect size estimate as the primary analysis (HR 1.24, 95%CI 0.99–1.55 for all RA). While the relatively more stringent components of the depression exposure were similarly associated with RA, we found no association of the survey measure of depressive symptoms with RA. This may be due to MHI-5 being measured earlier and less frequently in both cohorts compared to the other measures of depression. It is possible that only severe depression may impact RA risk, such that symptoms of low mood alone may not have a large impact on subsequent RA risk. It is also possible that the survey measure of depressive symptoms was too separated in time from the RA outcome assessment to impact risk (i.e., depressive symptoms in early adulthood may not impact postmenopausal RA risk).

While data were collected from nurses for research purposes, the clinical indication and adherence to medications was unclear. It is possible that women were using antidepressants for other indications such as pain, anxiety, fatigue, fibromyalgia, or sleep disturbance that may have been early manifestations of RA as well as other indications including other mental health disorders, menopausal symptoms, and smoking cessation. However, since we included a relatively long lag in analyses and were able to adjust for self-reported bodily pain, these measures were still predictive of future clinical RA diagnosis. While fibromyalgia was not systematically collected for all women in the analysis, only a relatively small proportion of RA cases were noted to have fibromyalgia at the time of RA diagnosis (9.0%), and results were not explained by self-reported bodily pain, which was collected on all women. When removing RA cases with fibromyalgia from the analysis, results remained similar. Therefore, we find it unlikely that fibromyalgia or pain explained our results. As we were unable to account for all possible indications of antidepressants, we acknowledge that the association of these medications with RA risk could be explained by their use for another purposes. Further studies are needed to investigate whether indications for antidepressants other than depression are associated with incident RA.

The documented median time from symptoms to diagnosis was only 6 months, much lower than the 4-year lag we used to protect against reverse causation. Therefore, we find it relatively unlikely that antidepressant use may have been for early RA symptoms, but we cannot fully rule out this possibility. PTSD was previously shown to be associated with RA risk(41), but this was only measured among a subset of women in the NHSII. It is possible that major stress life events could have explained some of the association of depression and RA risk, but we were unable to incorporate that variable into these analyses since it was not measured on all women. Future studies are needed to comprehensively examine multiple mental health domains for RA risk and other autoimmune diseases.

We extracted RF and anti-CCP results from medical records, but we had to rely on the accuracy and availability of clinical testing. Women diagnosed with RA prior to the 2000s may not have had anti-CCP results available so some patients may have been classified as seronegative solely based on RF results. However, our prior studies identified risk factors specific for seropositive RA(6) and seronegative RA(8), using similar methods. While we had detailed data on important confounders such as smoking pack-years, BMI, physical activity, and menopausal status, our findings still may be explained by residual unmeasured confounding. Finally, the NHS cohorts consist of female nurses who were educated, healthy, and working at enrollment. Therefore, our results may not be generalizable to other populations, such as men.

In conclusion, we demonstrated that depression may be associated with increased RA risk. Ours is the first study suggesting that depression may be a novel risk factor for seronegative RA. This excess risk was not explained by measured lifestyle factors or by early RA symptoms occurring within four years of clinical diagnosis. Since about one-third of patients with RA are seronegative, identification of risk factors and strategies to modify risk are urgently needed. While our findings should be considered hypothesis-generating, it is possible that patients with depression may be a population at risk for developing RA, potentially seronegative RA rather than seropositive RA. Future studies are needed to replicate our findings and to investigate potential biologic mechanisms linking indicators of depression such as antidepressant use with subsequent RA risk.

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SIGNIFICANCE & INNOVATIONS

- We investigated whether depression was associated with future risk of rheumatoid arthritis (RA) overall and by serostatus using the Nurses' Health Studies, two large cohort studies of women in the US.
- Previously reported associations of depression with increased RA risk may have been explained by early RA symptoms prior to diagnosis manifesting as depression. We included a separation of at least 4 years between when depression was assessed and the window for RA risk to limit this potential for reverse causation.
- Indicators of depression, specifically antidepressant use, were associated with increased risk for all RA and increased risk for seronegative RA, but there was no association of depression with seropositive RA.
- These results suggest that patients with depression, particularly those taking antidepressants, may be susceptible to developing seronegative RA years later, but further research is needed to confirm this novel finding.

Table 1.

Pooled age-standardized characteristics in 2000 in the Nurses' Health Study and 2001 in the Nurses' Health Study II (combined n=187,886) by depression* status.

	No depression (n=128,133)	Depression* (n=59,753)
Mean age**, years (SD)	56.1 (11.6)	52.4 (10.2)
White race, %	92.0	93.7
US geographic region, %		
West	21.3	21.9
Mid-Atlantic	34.5	32.3
Midwest	26.3	27.3
South	8.8	9.4
New England	9.2	9.2
Median household income, %		
Quartile 1 (lowest income)	23.8	25.1
Quartile 2	24.7	26.0
Quartile 3	25.3	24.9
Quartile 4 (highest income)	26.2	24.1
Smoking pack-year categories, %		
Never	57.9	50.9
1 to 10	17.4	17.9
>10 to 20	9.1	10.6
>20	14.3	19.3
Mean smoking pack-years among ever smokers (SD)	19.2 (17.9)	21.6 (20.0)
Body mass index category, %		
18.5 to <25 kg/m^2	45.8	39.7
25 to <30 kg/m^2	30.5	30.2
≥30 kg/m^2	21.4	28.3
Cumulative average Alternate Healthy Eating Index, %		
Quartile 1 (lowest quality)	21.8	25.6
Quartile 2	23.0	24.3
Quartile 3	23.5	23.7
Quartile 4 (highest quality)	24.3	22.7
Cumulative average physical activity <3 MET-hours/week, %	7.8	10.9
Parity/breastfeeding, %		
Nulliparous	10.2	12.5
Parous/<1 month	24.3	26.5
Parous/1–11 months	25.0	27.3
Parous/≥12 months	25.6	23.9
Menopausal status/postmenopausal hormone use, %		
Premenopausal	43.7	42.3
Postmenopausal/never	18.8	14.3
Postmenopausal/ever	37.6	43.4

	No depression (n=128,133)	Depression* (n=59,753)
Physical examination in past 2 years, %	79.2	85.7
Clinician-diagnosed depression, %	0.0	29.4
Regular antidepressant use, %	0.0	53.2
MHI-5 score <60, %	0.0	64.2

All three measures of depression were first assessed in 2000 in the NHS and 2001 the NHSII. The baseline of the primary analysis was 1992 in the NHS and 1993 in the NHSII, when MHI-5 was first assessed.

*Depression was defined as a composite of self-reported clinician-diagnosed depression, or regular antidepressant use, or MHI-5 score <60.

**Not age-standardized.

Missing data are not shown.

MET, metabolic equivalent of tasks; MHI, Mental Health Inventory; SD, standard deviation.

Table 2.

Description of incident rheumatoid arthritis cases in the primary analysis (n=858).

	All RA (n=858)	Seropositive RA (n=558)	Seronegative RA (n=300)
Median months from first symptoms to diagnosis (IQR) (n=119 missing)	6 (2, 12)	6 (2, 12)	7 (3, 13)
Diagnosed by ACR rheumatologist, n (%) (n=26 missing)	699 (81.5)	450 (80.7)	249 (83.0)
Radiographic changes/erosions, n (%)	222 (25.9)	139 (24.9)	83 (27.7)
Hand arthritis, n (%)	845 (98.5)	546 (97.9)	299 (99.7)
Symmetric arthritis, n (%)	829 (96.6)	530 (95.0)	299 (99.7)
≥3 joint areas affected, n (%)	780 (90.9)	492 (88.2)	288 (96.0)
>1 hour of morning stiffness, n (%)	648 (75.5)	390 (69.9)	258 (86.0)
Rheumatoid nodules, n (%)	59 (6.9)	48 (8.6)	11 (3.7)
Fibromyalgia at diagnosis, n (%) (n=32 missing)	44 (5.1)	17 (3.1)	27 (9.0)

ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MHI-5, Mental Health Inventory-5; RA, rheumatoid arthritis.

Table 3.

Hazard ratios for incident rheumatoid arthritis according to presence or absence of depression* among women in the Nurses' Health Studies (n=195,358), lagged by two questionnaire cycles (at least 4 years between depression and rheumatoid arthritis diagnosis assessments).

	No depression HR (95%CI)	Depression* HR (95%CI)
Outcome: All RA		
Case/person-years	549/2,208,144	309/879,412
Model 1 (age, demographics)**	1.00 (Ref)	**1.39 (1.20–1.61)**
Model 2 (age, demographics, health)**	1.00 (Ref)	**1.34 (1.16–1.56)**
Model 3 (age, demographics, health, behaviors)**	1.00 (Ref)	**1.28 (1.10–1.48)**
Outcome: Seropositive RA		
Case/person-years	366/2,206,177	192/878,527
Model 1 (age, demographics)**	1.00 (Ref)	**1.23 (1.03–1.48)**
Model 2 (age, demographics, health)**	1.00 (Ref)	1.19 (0.99–1.44)
Model 3 (age, demographics, health, behaviors)**	1.00 (Ref)	1.12 (0.93–1.35)
Outcome: Seronegative RA		
Case/person-years	183/2,204,059	117/877,569
Model 1 (age, demographics)**	1.00 (Ref)	**1.76 (1.37–2.24)**
Model 2 (age, demographics, health)**	1.00 (Ref)	**1.68 (1.31–2.15)**
Model 3 (age, demographics, health, behaviors)**	1.00 (Ref)	**1.63 (1.27–2.09)**

Bolded results have $p<0.05$.

The baseline of the primary analysis was 1992 in the NHS and 1993 in the NHSII, when MHI-5 was first assessed.

* Depression was defined as a composite of self-reported clinician-diagnosed depression, or regular antidepressant use, or MHI-5 score <60.

** Model 1 was adjusted for age, questionnaire cycle, cohort, and median household income

Model 2 was additionally adjusted for parity/breastfeeding, menopause/postmenopausal hormone use, and physical examination.

Model 3 was additionally adjusted for smoking pack-year category, body mass index category, Alternate Healthy Eating Index category, and sedentary physical activity.

CI, confidence interval; HR, hazard ratio; MHI, Mental Health Inventory, RA, rheumatoid arthritis.

Table 4.

Hazard ratios for incident rheumatoid arthritis according to presence or absence of depression* among women in the Nurses' Health Studies (n=190,715), lagged by three questionnaire cycles (at least 6 years between depression and rheumatoid arthritis diagnosis assessments).

	No depression HR (95%CI)	Depression* HR (95%CI)
Outcome: All RA		
Case/person-years	494/1,957,031	267/731,667
Model 1 (age, demographics)**	1.00 (Ref)	**1.41 (1.21–1.65)**
Model 2 (age, demographics, health)**	1.00 (Ref)	**1.37 (1.17–1.60)**
Model 3 (age, demographics, health, behaviors)**	1.00 (Ref)	**1.30 (1.11–1.52)**
Outcome: Seropositive RA		
Case/person-years	327/1,955,454	170/731,011
Model 1 (age, demographics)**	1.00 (Ref)	**1.30 (1.07–1.57)**
Model 2 (age, demographics, health)**	1.00 (Ref)	**1.27 (1.04–1.54)**
Model 3 (age, demographics, health, behaviors)**	1.00 (Ref)	1.19 (0.98–1.45)
Outcome: Seronegative RA		
Case/person-years	167/1,953,714	97/730,223
Model 1 (age, demographics)**	1.00 (Ref)	**1.67 (1.28–2.17)**
Model 2 (age, demographics, health)**	1.00 (Ref)	**1.60 (1.23–2.09)**
Model 3 (age, demographics, health, behaviors)**	1.00 (Ref)	**1.55 (1.18–2.02)**

Bolded results have $p<0.05$.

The baseline of the primary analysis was 1992 in the NHS and 1993 in the NHSII, when MHI-5 was first assessed.

* Depression was defined as a composite of self-reported clinician-diagnosed depression, or regular antidepressant use, or MHI-5 score <60.

** Model 1 was adjusted for age, questionnaire cycle, cohort, and median household income

Model 2 was additionally adjusted for parity/breastfeeding, menopause/postmenopausal hormone use, and physical examination.

Model 3 was additionally adjusted for smoking pack-year category, body mass index category, Alternate Healthy Eating Index category, and sedentary physical activity.

CI, confidence interval; HR, hazard ratio; MHI, Mental Health Inventory, RA, rheumatoid arthritis.

Table 5.

Hazard ratios for incident rheumatoid arthritis according to self-reported clinician-diagnosed depression, Mental Health Inventory (MHI)-5 score, or regular antidepressant use among women in the Nurses' Health Studies (n=195,358), lagged by two questionnaire cycles (at least 4 years between depression and rheumatoid arthritis diagnosis assessments).

	No clinician-diagnosed depression HR (95%CI)	Clinician-diagnosed depression HR (95%CI)
Outcome: All RA		
Case/person-years	490/1,684,399	97/239,610
Model 1 (age, demographics) *	1.00 (Ref)	**1.35 (1.08–1.69)**
Model 2 (age, demographics, health) *	1.00 (Ref)	**1.31 (1.05–1.64)**
Model 3 (age, demographics, health, behaviors) *	1.00 (Ref)	1.24 (0.99–1.55)
Outcome: Seropositive RA		
Case/person-years	324/1,683,287	64/239,449
Model 1 (age, demographics) *	1.00 (Ref)	**1.31 (1.00–1.72)**
Model 2 (age, demographics, health) *	1.00 (Ref)	1.29 (0.98–1.70)
Model 3 (age, demographics, health, behaviors) *	1.00 (Ref)	1.20 (0.91–1.58)
Outcome: Seronegative RA		
Case/person-years	166/1,682,018	33/239,231
Model 1 (age, demographics) *	1.00 (Ref)	1.43 (0.98–2.10)
Model 2 (age, demographics, health) *	1.00 (Ref)	1.37 (0.94–2.01)
Model 3 (age, demographics, health, behaviors) *	1.00 (Ref)	1.32 (0.90–1.94)
	No regular antidepressant use HR (95%CI)	**Regular antidepressant use HR (95%CI)**
Outcome: All RA		
Case/person-years	524/2,200,165	216/502,149
Model 1 (age, demographics) *	1.00 (Ref)	**1.71 (1.45–2.02)**
Model 2 (age, demographics, health) *	1.00 (Ref)	**1.65 (1.39–1.94)**
Model 3 (age, demographics, health, behaviors) *	1.00 (Ref)	**1.55 (1.31–1.83)**
Model 4 (age, demographics, health, behaviors, bodily pain) *	1.00 (Ref)	**1.37 (1.16–1.63)**
Outcome: Seropositive RA		
Case/person-years	355/2,198,462	132/501,602
Model 1 (age, demographics) *	1.00 (Ref)	**1.48 (1.20–1.82)**
Model 2 (age, demographics, health) *	1.00 (Ref)	**1.44 (1.17–1.77)**
Model 3 (age, demographics, health, behaviors) *	1.00 (Ref)	**1.34 (1.08–1.65)**
Model 4 (age, demographics, health, behaviors, bodily pain) *	1.00 (Ref)	1.21 (0.97–1.49)
Outcome: Seronegative RA		

Case/person-years	169/2,196,262	84/501,093
Model 1 (age, demographics) *	1.00 (Ref)	**2.26 (1.72–2.97)**
Model 2 (age, demographics, health) *	1.00 (Ref)	**2.13 (1.62–2.81)**
Model 3 (age, demographics, health, behaviors) *	1.00 (Ref)	**2.06 (1.56–2.72)**
Model 4 (age, demographics, health, behaviors, bodily pain) *	1.00 (Ref)	**1.75 (1.32–2.32)**
	Never MHI-5 score <60 HR (95%CI)	**Ever MHI-5 score <60 HR (95%CI)**
Outcome: All RA		
Case/person-years	671/2,347,197	164/545,719
Model 1 (age, demographics) *	1.00 (Ref)	1.03 (0.87–1.23)
Model 2 (age, demographics, health) *	1.00 (Ref)	1.02 (0.86–1.22)
Model 3 (age, demographics, health, behaviors) *	1.00 (Ref)	0.98 (0.82–1.17)
Model 4 (age, demographics, health, behaviors, antidepressant) *	1.00 (Ref)	0.89 (0.74–1.06)
Outcome: Seropositive RA		
Case/person-years	436/2,344,900	104/545,216
Model 1 (age, demographics) *	1.00 (Ref)	0.97 (0.78–1.21)
Model 2 (age, demographics, health) *	1.00 (Ref)	0.97 (0.78–1.20)
Model 3 (age, demographics, health, behaviors) *	1.00 (Ref)	0.92 (0.74–1.15)
Model 4 (age, demographics, health, behaviors, antidepressant) *	1.00 (Ref)	0.86 (0.68–1.07)
Outcome: Seronegative RA		
Case/person-years	235/2,342,577	60/544,617
Model 1 (age, demographics) *	1.00 (Ref)	1.15 (0.86–1.54)
Model 2 (age, demographics, health) *	1.00 (Ref)	1.13 (0.85–1.52)
Model 3 (age, demographics, health, behaviors) *	1.00 (Ref)	1.10 (0.82–1.47)
Model 4 (age, demographics, health, behaviors, antidepressant) *	1.00 (Ref)	0.95 (0.70–1.28)

Bolded results have $p<0.05$.

The baseline of the clinician-diagnosed depression analysis was 2000 in the NHS and 2001 in the NHSII. The baseline of the regular antidepressant use analysis was 1996 in the NHS and 2001 in the NHSII. The baseline of the MHI-5 analysis was 1992 in the NHS and 1993 in the NHSII.

* Model 1 was adjusted for age, questionnaire cycle, cohort, and median household income

Model 2 was additionally adjusted for parity/breastfeeding, menopause/postmenopausal hormone use, and physical examination.

Model 3 was additionally adjusted for smoking pack-year category, body mass index category, Alternate Healthy Eating Index category, and sedentary physical activity.

Model 4 was additionally adjusted for bodily pain quartile by MHI-5 (only for antidepressant analyses) and regular antidepressant use (only for MHI-5 analyses).

CI, confidence interval; HR, hazard ratio; MHI, Mental Health Inventory, RA, rheumatoid arthritis.

Table 6.

Multivariable* hazard ratios for incident rheumatoid arthritis according to presence or absence of depression in sensitivity analyses.

Sensitivity analysis**	HR (95%CI) for all RA	HR (95%CI) for seropositive RA	HR (95%CI) for seronegative RA
No lag between depression and RA assessments	**1.25 (1.09–1.42)**	1.11 (0.94–1.32)	**1.52 (1.22–1.89)**
One questionnaire cycle (2-year) lag between depression and RA assessments	**1.22 (1.06–1.40)**	1.07 (0.90–1.28)	**1.52 (1.20–1.91)**
Removal of 44 RA cases with fibromyalgia at diagnosis	**1.21 (1.04–1.41)**	1.09 (0.90–1.32)	**1.49 (1.14–1.94)**
Baseline of 2000 in the NHS and 2001 in the NHSII (when all 3 indicators of depressive were first assessed)	**1.30 (1.11–1.53)**	1.14 (0.94–1.39)	**1.69 (1.29–2.22)**
3-level time-updated depression variable	Current: **1.29 (1.10–1.52)** Past: 1.27 (0.99–1.61) Never depression: 1.00 (Ref)	Current: 1.11 (0.91–1.37) Past: 1.16 (0.86–1.57) Never depression: 1.00 (Ref)	Current: **1.69 (1.29–2.21)** Past: **1.51 (1.00–2.29)** Never depression: 1.00 (Ref)
Adjustment for covariates only as of baseline	**1.30 (1.21–1.62)**	1.13 (0.94–1.36)	**1.67 (1.31–2.15)**

Bolded results have $p<0.05$.

*Adjusted for age, questionnaire cycle, cohort, median household income, parity/breastfeeding, menopause/postmenopausal hormone use, and physical examination, smoking pack-year category, body mass index category, Alternate Healthy Eating Index category, and sedentary physical activity.

**Comparisons are between depression vs. no depression (reference) unless otherwise indicated.