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Association Between Depressive Symptoms and Incidence of Crohn's Disease and Ulcerative Colitis: Results From the Nurses' Health Study

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Abstract

BACKGROUND & AIMS—Depression and psychosocial stress are believed to contribute to the pathogenesis of Crohn's disease (CD) and ulcerative colitis (UC). Although many mechanisms have been proposed to link these disorders, few prospective studies have examined the relationship between depressed mood and incidence of CD or UC.

METHODS—We analyzed data from 152,461 women (aged 29–72 years) enrolled since 1992–1993 in the Nurses' Health Study cohorts I and II. Self-reported depressive symptoms were assessed by using the Mental Health Index (MHI)-5, a validated 5-item subscale of the 36-item Short-Form health survey, which is designed to estimate psychological distress on the basis of scores that range from 0 to 100. Self-reported CD and UC were confirmed through blinded record review by 2 gastroenterologists. Cox proportional hazards models were used to associate recent (within 4 years) and baseline MHI-5 scores with risk for CD or UC, adjusting for other risk factors.

RESULTS—During 1,787,070 person-years of follow-up, we documented 170 cases of CD and 203 cases of UC. Compared with women with recent MHI-5 scores of 86–100, women with recent depressive symptoms (MHI-5 scores <52) had an increased risk of CD (multivariate-adjusted hazard ratio [HR], 2.39; 95% confidence interval [CI], 1.40–3.98; *P* trend = .001). Baseline depressive symptoms, assessed from the baseline MHI-5 score, were also associated with CD, although with a lower HR (1.62; 95% CI, 0.94–2.77). Recent (HR, 1.14; 95% CI, 0.68–1.92) and baseline depressive symptoms were not associated with increased risk of UC (HR, 1.07; 95% CI, 0.63–1.83).

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CONCLUSIONS—On the basis of data from the Nurses' Health Study, depressive symptoms increase the risk for CD, but not UC, among women. Psychological factors might therefore contribute to development of CD. Further studies are needed to determine the mechanisms of this association.

Keywords

Inflammatory Bowel Disease; Stress; Epidemiology; Intestinal Inflammation

Inflammatory bowel diseases (IBDs) (Crohn's disease [CD], ulcerative colitis [UC]) are chronic immunologically mediated diseases that develop as a result of a dysregulated immune response to intestinal microflora in a genetically susceptible host.[1–4] The role of environmental factors influencing disease risk remains inadequately studied and poorly understood despite considerable epidemiologic evidence suggesting a strong role for such factors.

Psychosocial stress and depression have been purported to play a role in the pathogenesis of CD and UC.[5–10] Depression can influence risk of immune-mediated diseases through its effect on the hypothalamus-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS), systemic inflammatory cytokines, or immune cell function.[6,7,9,11] Studies examining the role of depression in IBD have primarily focused on those with established disease.[10] Patients with IBD experience an increased risk of anxiety and depression.[12–15] Inadequate coping mechanisms, stressful life events, and depression have all been associated with risk of disease relapse.[10] The few studies that have examined the role of mood in disease onset relied predominantly on the occurrence of major life events as a stressor, failed to adjust for possible confounders, did not specifically examine the role of depression, or ascertained outcome retrospectively after disease onset, raising the possibility of recall bias.[5,10,16,17]

To address these limitations, we investigated the association between remote and recent measures of depressive symptoms on subsequent risk of CD and UC in 2 large prospective cohorts of women, the Nurses Health Study (NHS) I and NHS II. These large cohorts provided a unique opportunity to prospectively assess validated measures of depression at several time points before diagnosis in relation to physician-confirmed diagnoses of incident CD and UC during long-term follow-up.

Methods

Study Population

The NHS I is a prospective cohort that enrolled 121,700 female registered nurses of age 30–55 years in 1976. The NHS II was a subsequent cohort established in 1989 that enrolled 116,686 female registered nurses of age 25–42 years. Both cohorts have been followed with biennial questionnaires, with a response rate consistently exceeding 90%. The present study included women who responded to the health-related quality of life assessment in 1992 (NHS I) or 1993 (NHS II). As has been described previously, women who responded to these surveys were similar in baseline characteristics to the full cohort (eg, age, body mass index [BMI], smoking, aspirin use, physical activity, and postmenopausal hormone [PMH] use).[18,19] We excluded women who reported a diagnosis of IBD or cancer (except nonmelanoma skin) before the study start date (1992 for NHS I and 1993 for NHS II). The study was approved by the Institutional Review Board of the Brigham and Women's Hospital.

Assessment of Depressed Mood

Depressive symptoms were assessed in 1992, 1996, and 2000 in the NHS I and in 1993, 1997, and 2001 in NHS II by using the 5-question Mental Health Index (MHI-5).[19–22] This is a subscale of the Short-Form 36 health status survey that includes 5 items designed to capture depressive symptoms and psychological distress. Respondents are asked how much of the time during the past month they felt (1) nervous, (2) calm and peaceful, (3) happy, (4) down and blue, and (5) so down that nothing could cheer them up. Each response is scored on a Likert scale from 1 (all of the time) to 6 (none of the time). The total score comprises the sum of the scores for each of the above questions, with the scores for the "positive" emotions—calm and peaceful, and happy—being scored as reverse. This score is then rescaled to assign an aggregate score from 0 to 100. Lower scores indicate greater degree of depressive mood. Consistent with prior analyses, women with scores between 0 and 52 were categorized as having depressive symptoms; women with scores between 86 and 100 comprised the referent group.[18,19,21] The MHI-5 has been shown to have good predictive value in identifying both depression and anxiety.[23] Beginning in 1993 in NHS II and in 1996 in NHS I, women were also asked whether they regularly used antidepressant medications; this information was subsequently updated biennially.

Ascertainment of Crohn's Disease and Ulcerative Colitis

Our methods for assessment of disease outcomes have been detailed in previous publications from our cohort.[24–26] In brief, since 1976 for NHS I and 1989 for NHS II, women were invited to self-report diagnosis of CD and UC on each biennial questionnaire. When a diagnosis was reported, a supplemental questionnaire was sent to request permission to obtain medical records as well as more detailed medical information. Medical records were reviewed by 2 independent gastroenterologists blinded to the exposure status. A diagnosis of CD or UC was assigned on the basis of the typical clinical presentation for 4 weeks or longer and established typical findings on endoscopic, histologic, radiological, or surgical evaluation consistent with a diagnosis of CD or UC. Disagreement between the reviewers was resolved through consensus. After 1992 in NHS I and 1993 in NHS II, a total of 1644 women from NHS I and 1409 women from NHS II self-reported a diagnosis of CD or UC. Among the 2290 women (84%) who were not deceased, did not report a diagnosis before 1976 or 1989, and could be contacted for the supplementary question, 837 (37%) denied the diagnosis on the basis of a more detailed description of the diseases, 906 women provided permission for medical record review, and 706 (78%) were confirmed as having CD, UC, or chronic/indeterminate colitis. For the present study, we excluded cases with chronic indeterminate colitis (n = 96), a diagnosis before 1992 in NHS I (n = 141) or 1993 in NHS II (n = 70), missing date of diagnosis (n = 24), and a history of cancer (n = 2), leaving 170 incident CD and 203 incident UC cases for analysis.

Covariates

Race and ethnicity was assessed in 1992 in the NHS I and 1989 in the NHS II and categorized as Caucasian, African, or Hispanic origin. Detailed information on cigarette smoking, weight, menopause status, use of oral contraceptives, PMHs, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs) was collected every 2 years.[24,27,28] BMI was computed by using weight in kilograms divided by height in square meters as reported at baseline. Participants' self-report of body weight and height has been previously validated.[29]

Statistical Analysis

Participants accrued follow-up time beginning on the date of return of the baseline questionnaire (1992 for NHS I and 1993 for NHS II) to the date of diagnosis of CD or UC,

death, or end of follow-up period, which ended on June 1, 2004, for NHS I and June 1, 2005, for NHS II, whichever came first. We used a Cox proportional hazards model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) while adjusting for potential confounding variables, including age, smoking, oral contraceptive use, PMH use, regular use of aspirin, NSAIDs, and BMI. The covariates included in our multivariate model were determined a priori on the basis of their known or suspected association with CD or UC or prior studies from our cohorts.[24,27,30] We used biennially updated information on smoking status, use of oral contraceptives, PMHs, aspirin, and NSAIDs. Because weight may be influenced by preclinical disease, we adjusted for BMI by using the baseline value, consistent with prior analyses.

Consistent with prior studies, we categorized the MHI-5 score into 4 groups (86 –100 [referent], 76 – 85, 53–75, and 0 –52, with the latter category being classified as depressed mood).[18,19,21] Recent depressive symptoms were assessed by using a questionnaire administered within 4 years (ie, the 1992 questionnaire for follow-up between 1992 and 1996). Remote depressive symptoms were assigned by using the earliest available MHI-5 score (1992 for NHS I and 1993 for NHS II) for the entire follow-up period (through 2004 – 2005). We observed no heterogeneity in the association of MHI-5 with either CD or UC in separate analyses of NHS I and NHS II (*P* for heterogeneity >.10 for both CD and UC). Thus, we pooled individual-level data from the 2 cohorts and adjusted for cohort in all analyses. In a lag analysis, to account for the effect of prediagnosis symptoms of IBD on psychological distress, we excluded patients diagnosed within 2 years of the first questionnaire and assigned MHI-5 values on the basis of questionnaires that allowed for a lag period of at least 2 years (range, 2– 4 years). Finally, to examine the potential confounding by antidepressant use, we repeated our analysis excluding patients who had reported antidepressant use. Information of any antidepressant use was first ascertained in 1996, with details regarding the specific antidepressant available only from 2000. We also repeated our analysis adjusting for use of antidepressants in our models. All models satisfied the proportionality of hazards assumption. We used SAS software 9.1 for all analyses (SAS Institute Inc, Cary, NC). A two-sided *P* value of <.05 was considered statistically significant.

Results

Among 66,815 women in NHS I and 85,646 women in NHS II, we documented 203 incident cases of UC and 170 incident cases of CD during 1,787,070 person-years of follow-up. In the combined cohort at baseline, the median age was 44.8 years (range, 28.5–72.3 years), and the median MHI-5 score was 76 (interquartile range, 64–84), with 16,986 women (11.1%) meeting the definition of depressed mood (MHI-5 ≤52) at baseline. Table 1 presents the baseline characteristics of the women according to MHI-5. Women who reported depressed mood were more likely to be younger and premenopausal, were less likely to have used oral contraceptive pills, or regularly use NSAIDs.

On the basis of the recent MHI-5 administered within 4 years, we observed a significant linear increase in risk of CD according to decreasing MHI-5 score ($P_{\text{linear trend}} = .001$) (*P* value for linear trend was calculated by modeling the median MHI-5 value for each stratum as a linear variable) (Table 2). Compared with women with a recent MHI-5 score of 86–100, the multivariate HRs for CD were 1.38 (95% CI, 0.90–2.13) for women with MHI-5 of 76–85, 1.59 (95% CI, 1.02–2.47) for women with MHI-5 of 53–75, and 2.36 (95% CI, 1.40–3.98) for women with a depressed mood (MHI-5 of 0–52). There was no association between depressed mood and UC (multivariate HR, 1.14; 95% CI, 0.68–1.91; $P_{\text{linear trend}} = .50$ for MHI-5 score).

To assess the influence of more remote mood, we also examined the association of the earliest assessment of MHI-5, the baseline survey, and incidence of CD and UC (Table 3). The median time from the baseline MHI-5 to diagnosis of CD or UC was 6 years (interquartile range, 4–10 years). Compared with women with a baseline MHI-5 of 86–100, the multivariate HR for CD was 1.62 (95% CI, 0.94–2.77) for women with depressed mood. The association between decreasing MHI-5 and increasing risk of CD was monotonic and statistically significant ($P_{\text{linear trend}} = .04$). In contrast, baseline MHI-5 score was not statistically associated with risk of UC ($P_{\text{linear trend}} = .67$). We did not observe any effect modification by known risk factors ($P > .05$ for all).

To account for the possibility that depressed mood may be a reflection of prediagnosis symptoms of CD or UC, we conducted a lag analysis in which we excluded cases of CD and UC diagnosed within 2 years of MHI-5 assessment. In these analyses, the association between depressed mood and CD (multivariate HR, 2.13; 95% CI, 1.15–3.95) and UC (multivariate HR, 1.31; 95% CI, 0.75–2.26) remained materially unchanged. We also conducted analyses restricting the cohort to follow-up after 1996 when we began routinely assessing the use of antidepressant medications. Adjusting for antidepressant use in the multivariate model slightly attenuated the effect sizes for depressed mood for CD (HR, 1.57; 95% CI, 0.85–2.90) and UC (HR, 1.02; 95% CI, 0.58–1.78). Excluding users of antidepressant therapy resulted in HRs of 2.53 (95% CI, 1.50–4.28) for women with depressed mood for CD and 2.05 (95% CI, 1.24–3.39) for UC. The HRs for antidepressant use itself were null for both CD (HR, 1.14; 95% CI, 0.66–1.97) and UC (HR, 1.22; 95% CI, 0.67–2.40) when adjusted for depressive symptoms.

Discussion

In 2 large prospective cohorts of women, we observed that depressive symptoms are associated with a 2-fold increase in risk of CD but not UC. Although both recent (within 4 years) and remote (baseline) assessments of depression appear to influence disease risk, the association with recent depressive symptoms appeared more prominent. We observed that the association of depressive symptoms with CD had effect sizes that were in the same range as those we found for current smoking,[30] oral contraceptive use,[27] and NSAID use.[24] Similarly, we observed comparable effect estimates for hormone replacement therapy and NSAID use with UC.[28] Our findings support the potential importance of a biopsychosocial model in the pathogenesis of CD and suggest the need for further studies on the effect of depression and stress on immune function and regulation.

Depression and life stress have been hypothesized to influence immune function and the risk and course of immune-mediated diseases including CD and UC.[5–9,17] Prior studies have demonstrated an increase in incidence of anxiety and depression among patients with IBD.[12] In addition, depression or life stress has been associated with disease flares in patients with CD and UC. Among 101 patients with CD in remission for up to 1 year, Bitton et al[31] reported that perceived stress and coping mechanisms were significant predictors of time to relapse. Similarly, among patients with UC, associations have been observed between higher stress and risk of relapse or mucosal inflammation.[32,33]

The few retrospective studies that have examined the association between psychological factors and risk of developing CD and UC have focused primarily on life stress rather than depressive symptoms and have observed inconsistent associations. In a case-control study of 167 cases of CD, 74 cases of UC, 69 controls with acute self-limiting colitis, and 255 healthy controls, both CD and UC cases had higher perceived stress, with CD, but not UC, cases experiencing more frequent stressful life events in the 6-month period before diagnosis compared with either control group.[5] In contrast, Tocchi et al[17] found that stressful life

events in the 12-month period before diagnosis were 4 times as common in those with newly diagnosed UC (44%) compared with controls (10.7%). The only prior prospective study was an analysis of 21,062 parents who lost a child compared with 293,745 who did not. During a 16-year follow-up there was no difference in first hospitalization for CD or UC between the 2 groups.[16] The inconsistent results of these studies compared with our findings may be attributable to the use of a traumatic event as a proxy for depressive symptoms or chronic stress, an assessment of stress limited to a single time point, and the inclusion of only severe cases that warranted hospitalization as end points.

A role of depression in influencing immune function and risk of IBD is biologically plausible. In a dextran sulfate sodium murine model of colitis, induction of depression by olfactory bulbectomy or intracerebroventricular injection of reserpine was associated with reactivation of inflammation in mice with previously established quiescent chronic inflammation. Moreover, this effect was mediated in part by an increase in proinflammatory cytokine secretion by macrophages.[34] Interestingly, administration of tricyclic antidepressants prevented reactivation of colitis among depressed mice but not nondepressed mice. In humans, depression is associated with elevated levels of C-reactive protein[35,36] and tumor necrosis factor–α,[37] key mediators of inflammation in patients with IBD. In addition, acute experimental stress can also increase interleukin (IL)-6, IL-10, IL-1β, and tumor necrosis factor–α production in response to stimulation by lipopolysaccharide.[7,11] Acute experimental stress or stressful life events can also alter number and function of CD4 and CD8 lymphocytes and natural killer as well as modulate platelet function and activation.[7,11] The effect of stress and depression may be mediated through the ANS through an effect on HPA axis stimulation, leading to production of cortisol, adrenaline, and noradrenaline. The ANS has been proposed to interact directly with immune cells because several inflammatory cells carry receptors for hormones of the HPA axis.[7] Such an interaction has been proposed to explain some of the immune effects of stress, including inflammatory cytokine production and platelet activation.

Our study has several strengths. First, we used a prospectively administered MHI questionnaire to ascertain depressive symptoms before development of CD and UC. A measure of depression and stress obtained before diagnosis is less likely to be prone to recall bias, the primary limitation of retrospective studies. Moreover, our validated MHI-5 assessments likely better capture chronic depressive symptoms across a broader range than use of single, traumatic life events. Second, because we updated our MHI-5 during follow-up, we were able to separately examine the effect of depressive symptoms during various latency periods between exposure and onset of IBD. Third, we had available information on a wide range of potential confounders, including use of antidepressants. Fourth, we used physician-confirmed cases of CD and UC as our outcomes, minimizing errors in ascertainment of outcome. Our cohort had high levels of medical knowledge, further improving the accuracy of assessment of exposures and confounding variables.

There are a few limitations to our study. First, the cohort consisted entirely of female nurses who were predominantly Caucasian. However, there are limited data to suggest that the effect of depression on disease risk varies according to gender, race, or occupation. CD and UC incidence rates in our cohort are comparable to those of other US populations, and our prior studies in the NHS I and II have yielded environmental risk factor associations consistent with the other cohorts.[24–27] Second, the median age of our cohort was 45 years. Thus, we are not able to examine the influence of depressive symptoms on risk of CD or UC in younger populations. However, our results are relevant to the many individuals who develop IBD in later life during the so-called second “bimodal” peak of age at diagnosis.[38] Third, our assessment of depressive symptoms was based on a limited, self-administered MHI. However, this brief survey is a validated measure of assessment of depression and

anxiety and has been associated with several other end points in these cohorts.[18–21] Fourth, although we used prospective data on mental health obtained before diagnosis, it is possible that preclinical symptoms of IBD, before a formal diagnosis, could account for our observed associations. However, our findings were robust in a lag analysis in which cases of IBD diagnosed within 2 years of an MHI-5 were excluded as end points. It is possible that women with a formal diagnosis of depression who were being treated with antidepressant medications may have been misclassified according to their MHI-5 score. However, sensitivity analyses in which we excluded women who used antidepressant medications did not materially alter our results. Moreover, such misclassification of depressed mood would be expected to bias our results toward the null. It is unlikely that there is significant confounding by antidepressant use, because excluding such patients resulted in a strengthening of our effect sizes, and HRs for antidepressant use itself were null. Finally, a larger number of confirmed incident cases may have yielded superior statistical power to define weaker associations such as may exist for remote depressive symptoms.

This study examined depressive symptoms ascertained prospectively with risk of CD and UC. Our results, in conjunction with animal models demonstrating the effect of stress on immune function, susceptibility to colitis, and human studies on the association between depression or stress and disease incidence and relapse, provide support to a biopsychosocial model of IBD pathogenesis in which the risk of development of disease is influenced by psychosocial factors. Preliminary animal and human studies suggest that treating depression through administration of antidepressants or through improvement in coping mechanisms could reduce risk of disease relapse.[6,8,34,39] Whether similar interventions can also influence risk of disease onset, particularly among individuals with genetic susceptibility for CD or UC, merits further study.

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Abbreviations used in this paper

ANS	autonomic nervous system
BMI	body mass index
CD	Crohn's disease
CI	confidence interval
HPA	hypothalamus-pituitary-adrenal
HR	hazard ratio
IBD	inflammatory bowel disease
IL	interleukin
MHI	Mental Health Index
NHS	Nurses Health Study
NSAID	nonsteroidal anti-inflammatory drug

PMH	postmenopausal hormone
UC	ulcerative colitis

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Table 1

Baseline Characteristics[a] of Study Population According to MHI-5 Score

	MHI-5 score 86–100 (n = 32,948)	MHI-5 score 76–85 (n = 53,870)	MHI-5 score 53–75 (n = 48,657)	Depressed mood 0–52 (n = 16,986)	Total (n = 152,371)
Mean age (standard deviation) (*y*)	51.2 (12.1)	47.4 (11.5)	45.8 (10.9)	44.5 (10.1)	47.4 (11.5)
White race (%)	97	97	97	97	97
Smoking status (%)					
Never smoker	60	57	54	51	56
Past smoker	30	32	32	32	31
Current smoker	10	11	14	17	12
Ever oral contraceptive use (%)	68	69	70	70	69
Premenopausal (%)	58	58	57	55	57
PMH use[b] (%)					
Never users	38	36	34	32	34
Past users	18	20	21	23	20
Current users	44	44	45	46	46
BMI (kg/m^2) (%)					
<20.0	14	14	14	13	14
20.0–24.9	50	50	48	45	49
25.0–29.9	23	23	24	24	23
≥30.0	13	13	14	18	14
Regular NSAID use ± (%)	16	18	19	20	18
Regular aspirin use ± (%)	21	22	21	21	21
Antidepressant use (%)[c]	4	7	12	24	10

±, regular use was defined as intake of 5 or more times per month.

[a] Baseline characteristics according to 1992 questionnaire for NHS I and 1993 questionnaire for NHS II.

[b] Percentages among postmenopausal women.

[c] Antidepressant use as ascertained in 1996 in NHS I and in 1993 in NHS II.

Table 2

Risk of CD and UC According to Recent MHI-5 Score[a]

	MHI-5 score 86–100	MHI-5 score 76–85	MHI-5 score 53–75	Depressive symptoms 0–52	*P* linear trend
Person-years of follow-up	478,480	616,292	516,500	175,798	
CD					
No. of cases	33	57	53	27	
Age-adjusted incidence[b]	7	9	10	15	
Age-adjusted HR (95% CI)	1.0	1.41 (0.91–2.17)	1.65 (1.06–2.57)	2.55 (1.51–4.29)	.0003
Multivariate HR (95% CI)[c]	1.0	1.38 (0.90–2.13)	1.59 (1.02–2.48)	2.36 (1.40–3.99)	.0010
UC					
No. of cases	48	68	65	22	
Age-adjusted incidence[b]	10	11	13	13	
Age-adjusted HR (95% CI)	1.0	1.07 (0.73–1.55)	1.19 (0.81–1.74)	1.19 (0.71–1.98)	.4000
Multivariate HR (95% CI)[c]	1.0	1.05 (0.72–1.53)	1.16 (0.79–1.70)	1.14 (0.68–1.92)	.4900

NOTE. *P* value for linear trend was calculated by modeling the median MHI-5 value for each stratum as a linear variable.

[a] Recent depressive symptoms refer to MHI administered within 4 years of follow-up.

[b] Per 100,000 person-years.

[c] Adjusted for age, cohort, race (white, nonwhite), smoking (never, past, current), BMI (<20, 20–24.9, 25–29, ≥30 kg/m^2), oral contraceptive use (never, past, current), use of PMH therapy (premenopausal, PMH never user, past user, current user), regular use of NSAIDs (yes, no), regular use of aspirin (yes, no).

Table 3

Risk of CD and UC, According to Baseline MHI-5[a]

	MHI-5 score 86–100	MHI-5 score 76–85	MHI-5 score 53–75	Depressive symptoms 0–52	*P* linear trend
Person-years of follow-up	385,462	632,548	570,487	198,573	
CD					
No. of cases	32	54	59	25	
Age-adjusted incidence[b]	8	9	10	13	
Age-adjusted HR (95% CI)	1.0	1.11 (0.72–1.73)	1.39 (0.90–2.16)	1.75 (1.03–2.99)	.02
Multivariate HR (95% CI)[c]	1.0	1.09 (0.70–1.69)	1.33 (0.86–2.06)	1.62 (0.95–2.77)	.04
UC					
No. of cases	38	70	73	22	
Age-adjusted incidence[b]	10	11	13	11	
Age-adjusted HR (95% CI)	1.0	1.10 (0.74–1.65)	1.25 (0.84–1.87)	1.11 (0.65–1.89)	.55
Multivariate HR (95% CI)[c]	1.0	1.09 (0.73–1.62)	1.22 (0.82–1.82)	1.07 (0.63–1.83)	.66

[a] Remote depressive symptoms refer to MHI-5 administered in 1992 (NHS I) or in 1993 (NHS II).

[b] Per 100,000 person-years.

[c] Adjusted for age, cohort, race (white, nonwhite), smoking (never, past, current), BMI (<20, 20–24.9, 25–29, ≥30 kg/m^2), oral contraceptive use (never, past, current), use of PMH therapy (premenopausal, PMH never user, past user, current user), regular use of NSAIDs (yes, no), regular use of aspirin (yes, no).