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Endometriosis and the risks of systemic lupus erythematosus and rheumatoid arthritis in the Nurses' Health Study II

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Abstract

Objectives—The etiologies of endometriosis, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are all characterized by immune dysfunction. SLE and RA occur more often in women, and reproductive and hormonal factors have been shown to be related to increased risk. However, only one previous study has evaluated the temporal association between endometriosis and SLE or RA. We sought to investigate the association between laparoscopically-confirmed endometriosis and subsequently diagnosed SLE and RA.

Methods—We analyzed data from the Nurses' Health Study II (n=114,453 women) over a 22-year follow-up period. Multivariable, time-varying Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the association between laparoscopically-confirmed endometriosis and confirmed incident SLE or RA.

Results—From 1989 to 2011, 103 incident cases of SLE and 390 cases of RA were confirmed. Laparoscopically-confirmed endometriosis was significantly associated with subsequent SLE

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diagnosis (HR=2.03; CI=1.17-3.51) and RA diagnosis (HR=1.41; CI=1.05-1.89). These associations were robust to adjustment for SLE or RA risk factors and for potential confounders, however, adjustment for hysterectomy and oophorectomy attenuated both relations such that they were no longer significant. No significant differences by infertility status or age (<45 years) were observed.

Conclusions—Our findings suggest an association between endometriosis and risk of SLE and RA. It remains to be understood whether and how endometriosis itself, or hysterectomy or other factors associated with endometriosis, are related to risk of SLE or RA.

Keywords

endometriosis; systemic lupus erythematosus; rheumatoid arthritis; epidemiology

Introduction

Endometriosis is defined as the presence of endometrial tissue external to the uterine cavity. There is strong circumstantial evidence that, perhaps synergistically with circulating steroid hormones, endometriosis is dependent on immunologic abnormalities.[1] The systemic connective tissue diseases – including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) – are inflammatory rheumatic diseases of immunologic origin. While the etiology of these diseases are incompletely understood, both primarily affect women, who represent 60% or more of RA cases[2 3] and up to 90% of SLE cases[3 4]. In addition, reproductive and hormonal factors have been associated with risk of SLE and RA.[2-9]

Case reports have suggested co-morbidity of endometriosis with the autoimmune disorders alopecia universalis, autoimmune thyroiditis, multiple sclerosis, and autoimmune progesterone dermatitis,[10 11] and a comparative evaluation of clinical and humoral immunologic abnormalities between SLE and endometriosis has also suggested similarities.[12] A cross-sectional survey of women with endometriosis who were members of a national endometriosis support organization, compared to the general U.S. population, reported a prevalence odds ratio for SLE of 20.7 (CI=14.3-29.9) and for RA of 1.5 (CI=1.2-1.9);[13] however this survey was limited by its highly self-motivated study population with self-reported endometriosis and autoimmune diseases and lack of control for confounders. More recently, a retrospective cohort study in Denmark reported an increased risk of SLE among women with endometriosis (standardized incidence ratio [SIR] = 1.6; CI = 1.2-2.1). This association, however, was attenuated and non-significant when restricted to surgically-verified endometriosis cases.[14]

In the current study, we investigated the association between laparoscopically-confirmed endometriosis and the development of SLE and RA during 22 years of follow-up in the Nurses' Health Study II cohort.

Methods

Study population

The Nurses' Health Study II (NHS II) is an ongoing prospective cohort that was established in 1989 when 116,430 female registered nurses, ages 25 to 42, completed a baseline questionnaire on demographic and lifestyle factors, anthropometric variables, and disease history. Follow-up questionnaires have been sent biannually to participants. Further details on the study have been provided elsewhere.[15] This study was approved by the Institutional Review Boards of the Harvard School of Public Health and Brigham and Women's Hospital, Boston, Massachusetts.

Identification of endometriosis

Starting in 1993, participants were asked on each biennial questionnaire if they had “ever had physician-diagnosed endometriosis,” and, if so, the date of diagnosis and whether it had been confirmed by laparoscopy. The validity of self-reported endometriosis was examined in this cohort in March 1994. Two hundred of the 1,766 women who reported an incident diagnosis of endometriosis were randomly selected to complete a supplementary questionnaire and were asked for permission to review their medical records. A diagnosis of endometriosis was confirmed in 96% of those who reported laparoscopic confirmation and for whom medical records were reviewed (n=105). However, a review of the medical records of those without laparoscopic confirmation indicated a clinical diagnosis of endometriosis in only 54% (n=26). Among women who were diagnosed with endometriosis at the same time as they reported a hysterectomy, endometriosis was the primary indication for hysterectomy in only 6% of (n=9/163) of those for whom an indication was available.[16] Therefore, in order to minimize the magnitude of misclassification and prevent confounding by indication for hysterectomy, we restricted our definition of diagnosis of endometriosis to women who reported laparoscopic confirmation of their diagnosis.

Identification of SLE and RA

Incident self-reported doctor-diagnosed SLE and RA cases were identified and confirmed using a two-stage procedure described in detail elsewhere.[5] Briefly, participants who reported any connective tissue disease (CTD), including SLE and RA, on a biennial questionnaire received a previously validated Connective Tissue Disease Screening Questionnaire (CSQ).[17] Those who screened positive were asked for permission to have their medical records reviewed by two board-certified rheumatologist using the American College of Rheumatology (ACR) diagnostic criteria for RA[18] and SLE.[19 20] Cases were considered confirmed if they met ACR criteria and both reviewers agreed on the diagnosis. The case confirmation rates from medical record review were 69% for SLE with positive CSQ and 29% for RA with positive CSQ, and 7% of the original self-reports of SLE or RA. [5 21] This is nearly identical to the self-reported RA case confirmation rate for another prospective female cohort, the Iowa Women's Health Study,[22] highlighting the importance of the two-stage validation procedure. All self-reports of prevalent CTD at cohort entry were excluded and self-reports not subsequently confirmed as SLE or RA were censored at the date of diagnosis.

Statistical analysis

Participants contributed follow-up time from the return of the 1989 questionnaire until report of SLE or RA, report of any CTD not confirmed as SLE or RA, diagnosis of any cancer (except non-melanoma skin cancer), death, loss to follow-up, or end of follow-up on June 1, 2011, whichever occurred first. We used Cox proportional hazards regression models with age and questionnaire period as the time scale to estimate hazard rate ratios (HR), and 95% confidence intervals (CI) of incident confirmed SLE or RA in participants with endometriosis compared to those without. Both prevalent (diagnosed before the start of the cohort) and incident (diagnosed after study enrollment) cases of laparoscopically-confirmed endometriosis were included for the main analyses. Secondary analyses were conducted restricted to only incident (diagnosed after 1989) endometriosis cases. Exposures and covariates were time-varying - updated throughout the follow-up whenever new information was available from the biennial questionnaires from enrollment until the individual was censored.

We defined potential confounders as factors potentially associated with both endometriosis and SLE or RA risk including age at menarche, parity, menstrual cycle length, BMI, physical activity, smoking, oral contraceptive use, race/ethnicity, infertility, and analgesic use. For analyses of RA risk, multivariable models included the covariates above plus parity/total duration of breastfeeding. As hysterectomy, oophorectomy, oral contraceptive (OC) use, and postmenopausal hormone (PMH) use have the potential to be both confounders and mediators of the endometriosis and SLE or RA associations we examined their influence in two ways. First, we adjusted for each of these variables to examine them as potential confounders. Second, we applied the difference method of mediation analysis to calculate the proportion of association between SLE or RA and endometriosis statistically accounted for by each of these variables[23 24]. Finally, effect modification by age and infertility was assessed with a likelihood ratio test that compared the model with the cross-product term between the exposure variable and each potential effect modifier to the model with main effects only.

In a secondary analysis, we examined the association with confirmed SLE or RA as the exposure and laparoscopically-confirmed endometriosis as the outcome. This analysis differed from the main analysis, because participants were censored at report of hysterectomy or menopause since the occurrence of newly diagnosed endometriosis is rare after these events. All statistical analyses were performed using SAS Version 9.2 (SAS Institute Inc, Cary, NC).

Results

Compared to women without endometriosis, women with laparoscopically-confirmed endometriosis were older, more likely to have ever used oral contraceptives, more often nulliparous, more likely to have had a hysterectomy or oophorectomy, and more likely to report analgesic use of two or more days per week (Table 1). Diagnosis of SLE or RA occurred from 0.6 to 16.6 years following endometriosis diagnosis with a median time of 6.2 years for SLE and 7.0 years for RA.

In the analysis with endometriosis as the exposure and SLE as the outcome, 103 incident cases of SLE were reported during 1,986,867 person-years of follow-up. Laparoscopically-confirmed endometriosis was significantly associated with increased risk of SLE in age-adjusted (HR=2.05; CI=1.19-3.50) and multivariable-adjusted models (HR=2.03; CI=1.17-3.51). This association was attenuated with adjustment for hysterectomy (HR=1.72; CI=0.96-3.08), oophorectomy (HR=1.74; CI=0.96-3.15), and analgesic use (HR=1.91; CI=1.10-3.30) (Table 2), while adjustment for oral contraceptive use and postmenopausal hormone use did not substantially alter the association (results not shown). When the association was restricted to incident endometriosis cases the point estimates were slightly higher but with wider confidence intervals (HR=2.65; CI=1.19-5.89; hysterectomy adjusted HR=2.20; CI=0.96-5.04; oophorectomy adjusted HR=2.25; CI=0.97-5.23; analgesic adjusted HR=2.51; CI=1.13-5.58).

Mediation analysis revealed that 23% of the association between endometriosis and SLE was attributable to hysterectomy and 22% to oophorectomy; however, neither of these mediation associations was statistically significantly (p=0.22, and p=0.27, respectively). The association between endometriosis and SLE was strongest among women ≤45 years (HR=2.11; CI=1.06-4.19) and among those with a history of infertility (HR=2.41; CI=1.11 -5.24), although the interactions with age and with infertility were not statistically significant ($p_{interaction}$=0.86 and 0.44, respectively) (Table 3).

In the analysis with endometriosis as the exposure and RA as the outcome, 390 incident cases of RA were reported during 1,985,829 person-years of follow-up. Endometriosis was significantly associated with RA in the age-adjusted (HR=1.46; CI=1.10-1.95) and multivariable-adjusted models (HR=1.41; CI=1.05-1.89) (Table 2). This association was attenuated with adjustment for hysterectomy (HR=1.25; CI=0.92-1.71), oophorectomy (HR=1.22; CI=0.89-1.67), and analgesic use (HR=1.34; CI=1.00-1.80), while adjustment for OC use and PMH use did not substantially alter the association. When the association was restricted to incident endometriosis cases, the point estimates were similar but with wider confidence intervals (HR=1.36; CI=0.85-2.17; hysterectomy adjusted HR=1.18; CI=0.73-1.92; oophorectomy adjusted HR=1.14; CI=0.70-1.86; analgesic adjusted HR=1.31; CI=0.82-2.09).

Mediation analysis demonstrated that 35% of the association between endometriosis and RA was attributable to hysterectomy and 43% to oophorectomy, each with borderline statistical significance (p=0.09 and p=0.09, respectively). Similar to the SLE result, the association between endometriosis and RA was strongest among younger women (HR=1.48; CI=0.94-2.33), while in contrast to the SLE result the association between endometriosis and RA was strongest among women with no history of infertility (HR=1.64; CI=1.13-2.37). However, again the p-values for interaction were not significant ($p_{interaction}$=0.79 and 0.33, respectively) (Table 3).

In the secondary analyses examining laparoscopically-confirmed endometriosis as the outcome and confirmed SLE and RA as the exposures, numbers were quite small limiting the power to examine these associations. Two women with SLE were subsequently diagnosed with endometriosis among 4,597 incident endometriosis cases with a HR of 1.75

(CI=0.44-7.06). Four women with RA had a subsequent diagnosis of endometriosis with a HR of 1.58 (CI=0.59-4.23).

Discussion

In this large prospective cohort, we observed statistically significant associations between laparoscopically-confirmed endometriosis and risks of both SLE and RA, however, these associations were slightly attenuated and borderline significant following adjustment for hysterectomy and oophorectomy. For RA, hysterectomy and oophorectomy mediated the association, suggesting an indirect effect of endometriosis on RA risk may occur through hysterectomy and oophorectomy.

Few studies have evaluated the co-occurrence of endometriosis and autoimmune diseases including SLE and RA. Sinaii, et al. conducted a cross-sectional survey among 3,680 members of the Endometriosis Association with endometriosis. Compared to the general U.S. population, the prevalence odds ratio for SLE was 20.7 (CI=14.3-29.9) and for RA was 1.5 (CI=1.2-1.9).[13] However, this survey was self-reported and conducted among a membership dues paying study population who all reported experiencing moderate to severe pain symptoms. It differs from the typical clinical presentation of patients with endometriosis where a proportion are asymptomatic until diagnosed during an investigation of infertility or incidentally during pelvic surgery for other indications. In the present cohort of nurses, the confirmation of self-reported endometriosis in the absence of laparoscopy was 54% and the confirmation of self-reported SLE and RA was only 7%. Therefore, self-reports from the general population are likely highly misclassified. Finally, neither temporality nor confounding factors were considered in the past analyses.

In contrast to these findings, a Spanish case-control study based on clinical records, reported no significant difference in the prevalence of SLE among women with histologically confirmed endometriosis (n=342) compared to controls (n=501) (OR=0.37; CI=0.09-1.59).[25] The most recent study to date examined a retrospective cohort of women identified with endometriosis (n=37,661) through the Danish Hospital Discharge Register. A significant increased risk of SLE (SIR=1.6; CI=1.2-2.1) was observed, however this association was attenuated and non-significant when restricted to 9,191 women with surgically-verified endometriosis (SIR=1.1; CI=0.6-2.1).[14] To our knowledge, no studies besides Sinaii, et al. have examined the association between endometriosis and RA.

We observed that endometriosis and future SLE are associated, but that this association is confounded by hysterectomy, oophorectomy, and analgesic use. Endometriosis was also associated with a lesser magnitude with RA risk, and this association was similarly influenced by hysterectomy, oophorectomy, and analgesic use. The hazard ratios were similar when SLE and RA were considered exposures and laparoscopically-confirmed endometriosis was considered the outcome, however small numbers in this analysis limited power thus confidence intervals were quite wide. Given the overlapping age-incidence curves, we conducted these complementary analyses to examine the temporality of the associations, which for these diseases can be difficult to determine as they develop slowly over years and can have diagnostic delays. Perhaps the associations are primarily explained

by a common influence of hormonal factors and immunologic abnormalities, although in these analyses little confounding was observed after adjustment for reproductive history and other hormonal factors.

Women with endometriosis exhibit altered immune surveillance with depressed cell-mediated immunity (high T-, B-, and natural killer cell counts but decreased activity) and heightened humoral immune response (high serum levels of IgG, IgA, IgM auto antibodies, and anti-endometrial antibodies).[26 27] Like endometriosis, patients with SLE and RA have elevated humoral responses and abnormally increased and dysregulated antibody production, and these abnormalities can precede clinical diagnosis.[5 9 28-32] In addition, antinuclear antibodies (ANA), common in women with SLE,[33] have also been observed in women with endometriosis.[12 34] Elevation of inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), is observed in women with endometriosis.[35-41] Similarly, both SLE and RA are characterized by elevations in the concentrations of these systemic inflammatory cytokines.[42 43] The relationships between these enigmatic diseases and the systemic inflammation associated with each are not understood. However, the observation of an increased risk of RA and SLE among women with endometriosis points to a potential underlying shared pathogenesis that deserves further study.

Reproductive and hormonal factors also likely play roles in the etiologies of endometriosis, SLE, and RA. Hormonal influences on endometriosis are evident from the timing of symptoms that typically appear after menarche and end with menopause, as well as the efficacy of hormonal treatments including oral contraceptives.[44] Early menarche, exogenous hormone use, including both oral contraceptives and hormone replacement therapy (HRT), and surgical menopause have been associated with risk of SLE.[5 7] The peak incidence of RA in women occurs between ages 45-55, which may indicate a possible link between lower estrogen levels and disease onset.[6 8 9] Unlike SLE, most, but not all studies, have shown decreased risks of RA with OC use,[7 21 45 46] and decreased or no risk reduction with HRT use.[7 21 45] However, similar to SLE, a higher risk of RA was recently observed among women in the NHS II with surgical menopause.[47]

The similarities between the underlying humoral immune dysfunction observed in SLE and endometriosis and the similar direction of associations between hormonal risk factors in these two diseases may explain why a stronger association was observed between endometriosis and SLE compared to endometriosis and RA. In addition, as RA has a later average age of onset than SLE, a longer follow-up time may be necessary to observe a clear association between endometriosis and RA.

The treatment of endometriosis may influence the long-term risk of other diseases. To address this, we considered oral contraceptive use, postmenopausal hormone use, hysterectomy, and oophorectomy as potential confounders or mediators in the association between endometriosis and SLE or RA. Oral contraceptives are a common first-line empiric treatment for suspected endometriosis.[48] There is evidence that OC use may increase risk of SLE[5 7], but they have not been reported to increase RA risk.[7 21 45 46] However,

adjustment for OC use did not substantially alter the associations observed for endometriosis and SLE or RA and no mediation was observed.

Women with endometriosis are more likely to have a hysterectomy and/or oophorectomy and at an earlier age than women without endometriosis. We have previously observed increased risks of SLE associated with surgical menopause (hysterectomy with bilateral oophorectomy) and postmenopausal hormone use in the Nurses' Health Study[5] and an increased risk of RA with surgical menopause in the NHS II.[47] In the current analyses, adjustment for hysterectomy and oophorectomy attenuated the results, while adjustment for PMH use did not materially alter the associations. In the mediation analyses, the association between endometriosis and SLE was not statistically significantly mediated by hysterectomy; however, 35% of the association between endometriosis and RA was attributable to the high rate of hysterectomy among women with endometriosis (p=0.09).

Analgesic use, including non-steroidal anti-inflammatory drugs (NSAIDs), is a first line treatment for endometriosis[48] and adjustment for use of analgesics attenuated the associations with SLE and RA. Analgesic use is associated with SLE and RA risk among women in this cohort, likely due to being used to treat pain symptoms that occur before clinical diagnosis of SLE and RA, thus is likely a confounder of the associations with endometriosis, known as confounding by indication. The association between endometriosis and both SLE and RA was of the greatest magnitude among women ≤45 years old. SLE is a heterogeneous disease and late-onset SLE may have different manifestations and clinical characteristics than SLE diagnosed in younger patients.[49] In addition, it is possible that endometriosis is a stronger risk factor for SLE and RA in younger women, but, as women age, other age-related or accumulated factors more strongly influence risk.

Limitations must be considered when interpreting our results. Typically when examining incidence of laparoscopically-diagnosed endometriosis, it is ideal to evaluate the associations by infertility status as women who are diagnosed with endometriosis during an infertility evaluation will include women who are “asymptomatic” while women with no infertility are all “symptomatic” with respect to pain. However, even within this large cohort, numbers of SLE and RA cases were too small to stratify by infertility status when endometriosis was examined as the outcome. We were able to stratify by infertility history in the main analyses and observed a much stronger association between endometriosis and SLE among women with a history of infertility.

In addition, diagnostic delay from symptom onset to definitive diagnosis can be lengthy for endometriosis, SLE, and RA, making establishment of temporality for causal inference difficult. The average duration of symptoms prior to surgical diagnosis of endometriosis is seven years in the general population,[50] with the delay being slightly shorter in this cohort of nurses. SLE may also have a similar lag between initial symptoms and clinical diagnosis. However, when we examined the associations with endometriosis as the outcome, the results were similar although with much wider confidence intervals. No data within any study design currently exist to assess the time between disease initiation/establishment and emergence of clinical symptoms.

Our study has several important strengths. SLE and RA cases were determined using a two-stage validation procedure that included medical record reviews and all endometriosis cases were laparoscopically-confirmed. The large sample size and prospective design with 22 years of follow-up provided an ideal setting in which to study the association between these diseases, as data on many important covariates, including known risk factors for endometriosis, SLE, and RA, were collected and updated at two-year intervals.

In conclusion, our findings suggest associations between endometriosis and both SLE and RA. It remains to be understood whether and how endometriosis itself, or hysterectomy/oophorectomy or other factors associated with endometriosis, are related to risk of SLE or RA. Thus extended follow-up in this cohort and future research in a large collaborative consortium may help clarify these associations.

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Table 1

Age-standardized baseline characteristics of women in the Nurses' Health Study II in 1989 by laparoscopically-confirmed endometriosis

	Laparoscopically-confirmed endometriosis	
	No (n=108,019)	**Yes (n=6,434)**
Age (years)[1]	36.3(4.7)	37.8(4.2)
Caucasian, %	94.2	96.2
BMI (kg/m^2)		
<25, %	69.8	71.1
25-29.9, %	18.6	19.0
30+, %	11.6	9.9
Smoking status		
never, %	65.3	64.2
past, %	21.3	21.2
current, %	13.3	14.6
Age at menarche		
<12 years, %	24.4	28.6
12 years, %	30.1	29.8
13 years, %	27.4	26.4
>13 years, %	18.1	15.1
Menstrual cycle length		
<26 days, %	11.8	12.8
26-31 days, %	66.0	66.5
32-50 days, %	16.8	15.1
51+ and irregular, %	5.4	5.6
Ever use of oral contraceptives, %	82.9	88.9
Nulliparous, %	29.8	39.4
Ever infertile, %	16.5	48.8
Hysterectomy, %	4.2	21.6
Oophorectomy		
Unilateral, %	0.6	3.5
Bilateral, %	1.1	13.1
Menopausal status		
Premenopausal, %	97.8	85.5
Postmenopausal, %	1.6	13.7
Ever use of postmenopausal hormones, %	9.9	31.1
Analgesic use (≥2 days/week), %	40.9	51.2

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

Values of polytomous variables may not sum to 100% due to rounding

[1] Value is not age adjusted

Table 2

Hazard ratios and 95% confidence intervals of SLE and RA according to laparoscopically-confirmed endometriosis, Nurses' Health Study II, 1989-2011

	Laparoscopically-confirmed endometriosis	
Outcome	**No**	**Yes**
SLE[1]		
Cases	87	16
Person-years	1808556	178311
Age-adjusted model	1.00	2.05 (1.19-3.50)
Multivariable model	1.00	2.03 (1.17-3.51)
Multivariable model plus adjustment for hysterectomy	1.00	1.72 (0.96-3.08)
Multivariable model plus adjustment for oophorectomy	1.00	1.74 (0.96-3.15)
Multivariable model plus adjustment for analgesic use	1.00	1.91 (1.10-3.30)
Multivariable model adjusted for all variables above	1.00	1.61 (0.88-2.92)
RA[2]		
Cases	337	53
Person-years	1807611	178218
Age-adjusted model	1.00	1.46 (1.09-1.95)
Multivariable model	1.00	1.41 (1.05-1.89)
Multivariable model plus adjustment for hysterectomy	1.00	1.25 (0.92-1.71)
Multivariable model plus adjustment for oophorectomy	1.00	1.22 (0.89-1.67)
Multivariable model plus adjustment for analgesic use	1.00	1.34 (1.00-1.80)
Multivariable model adjusted for all variables above	1.00	1.16 (0.84-1.59)

SLE, systemic lupus erythematosis; RA, rheumatoid arthritis

[1]SLE model adjusted for pack years of smoking (continuous), age at menarche (<10, 10, 11, 12, 13, 14, 15, ≥16 years), oral contraceptive use (never, past, current), BMI (<19.0, 19.0-20.4, 20.5-21.9, 22.0-24.9, 25.0-29.9, ≥30 kg/m2), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, 27-41.9, ≥42 MET hours/week), race/ethnicity (Caucasian, other), and infertility (yes, no).

[2]RA model adjusted for the covariates above plus parity/total duration of breast feeding (nulliparous, parous/no breastfeeding, parous/breast feeding 1-11 months, parous/breast feeding 12+ months).

Table 3

Hazard ratios and 95% confidence intervals of SLE and RA according to laparoscopically-confirmed endometriosis by age and infertility history

Age	**≤45 years**	**>45 years**	**$p_{interaction}$[1]**
SLE[2]			
Number of cases	71	32	
Multivariable-adjusted[1]	2.11 (1.06-4.19)	1.91 (0.78-4.67)	0.86
RA[3]			
Number of cases	186	204	
Multivariable-adjusted[1]	1.47 (0.94-2.31)	1.37 (0.93-2.01)	0.81
Infertility history	Yes	No	
SLE[2]			
Number of cases	28	75	
Multivariable-adjusted[1]	2.41 (1.11-5.24)	1.54 (0.66-3.57)	0.44
RA[3]			
Number of cases	92	298	
Multivariable-adjusted[1]	1.21 (0.74-1.97)	1.64 (1.13-2.37)	0.33

[1] P-values for the interaction test were calculated by a likelihood ratio test comparing the model with main effects only with the model with the interaction terms.

[2] SLE model adjusted for pack years of smoking (continuous), age at menarche (<10, 10, 11, 12, 13, 14, 15, ≥16 years), oral contraceptive use (never, past, current), BMI (<19.0, 19.0-20.4, 20.5-21.9, 22.0-24.9, 25.0-29.9, ≥30 kg/m2), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, 27-41.9, ≥42 MET hours/week), race/ethnicity (Caucasian, other), and infertility (yes, no) except when stratified by infertility.

[3] RA model adjusted for the covariates above plus parity/total duration of breast feeding (nulliparous, parous/no breastfeeding, parous/breast feeding 1-11 months, parous/breast feeding 12+ months).