Early Life Factors and Adult-onset Rheumatoid Arthritis

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ABSTRACT. *Objective.* Early life factors have been associated with risk of developing autoimmune disease in adulthood. We investigated the association of preterm birth and being breastfed with the incidence of rheumatoid arthritis (RA) in 2 large prospective cohorts.

Methods. We studied participants from the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII) who provided information on perinatal factors. The NHS (n = 121,701) and NHSII (n = 116,608) are large prospective cohorts of women followed since 1976 and 1989, respectively. Incident RA was confirmed using the American College of Rheumatology criteria and a medical record review. Cox models were used to estimate the hazard ratio of RA associated with being born preterm and being breastfed and its duration, adjusting for potential confounders. Random effects metaanalytic methods were used to compute combined estimates from the 2 cohorts.

Results. We found no statistically significant association between preterm birth and incident RA [relative risk (RR) = 1.1, 95% CI 0.8, 1.5]. Being breastfed was not associated with increased incidence of RA (RR = 1.0, 95% CI 0.7, 1.4), regardless of the duration of breastfeeding.

Conclusion. In these cohorts of women, neither being preterm birth nor being breastfed was associated with the onset of RA. (J Rheumatol First Release Oct 15 2009; doi:10.3899/jrheum.090237)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   EARLY LIFE FACTORS   ADULT-ONSET
NURSES' HEALTH STUDY   PRETERM BIRTH   BREASTFEEDING

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Rheumatoid arthritis (RA) is 3 to 5 times more prevalent in women and its incidence increases with age[1]. It is hypothesized that the pathogenesis of RA may be related to early life factors such as birth weight and breastfeeding, which contribute to development and shaping of the immune system[2].

Recent population-based case-control studies investigated a number of perinatal factors in association with RA[3,4]. Breastfeeding that started in the hospital after delivery was associated with a dramatic 80%–90% lower incidence of RA with a median age at onset of 46 years, suggesting that exposure to breast milk during this period may affect the state of the immune system and in turn, influence the risk of autoimmunity later in life, including in adulthood[4]. Whether continuation of breastfeeding after hospital discharge is associated with RA risk has not been studied. In addition, rheumatoid factor (RF), an antibody associated with RA, was inversely associated with breastfeeding in an otherwise healthy pediatric population[5]. Gestational age, which may be related both to fetal exposures such as maternal smoking or exposure to infection and *in utero* maturation, did not appear to be significantly associated with RA[3,4]. However, high birth weight, possibly a reflection of *in utero* exposures, was associated with an increased risk of RA[4]. This finding was replicated in one[6], but not all studies[3]. We therefore considered the role of 2 other perinatal factors, preterm birth and having been breastfed, in RA incidence in 2 large

prospective cohorts, the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII). In these cohorts high birth weight and preterm birth were recently found to be risk factors for adult-onset systemic lupus erythematosus, a related rheumatic autoimmune condition[7].

MATERIALS AND METHODS

Study population. Established in 1976 with 121,701 initially recruited participants aged 30 to 55 years, the NHS collects extensive data biennially from female nurses across the US. In 1989 a second, similarly designed cohort of 116,608 female nurses aged 25 to 42 years were enrolled in NHSII. Details of these cohorts have been reported[8-10]. In the present study we excluded those who reported other systemic rheumatic diseases at cohort baseline, had missing diagnosis date, or self-reported RA that was not confirmed (NHS, n = 837; NHSII, n = 573). We further excluded those who did not complete the questionnaire that ascertained exposures during infancy (NHS, n = 27,803; NHSII, n = 8991) — the primary reason for not completing the series of questions about perinatal exposures was death or loss to followup — rather than selectively ignoring the questions. Additionally, anyone who did not report being a singleton birth (i.e., not part of a multiple birth) was excluded as the fetal environment for twins is different from singletons and data to further characterize these multiple births as monozygotic or dizygotic were missing (NHS, n = 6623; NHSII, n = 8913). An additional 123 records from NHS were excluded due to data inconsistencies. Thus 86,315 NHS and 98,131 NHSII participants were included in our study population.

Perinatal exposures. Preterm birth. In the 1991 NHSII and 1992 NHS questionnaires participants were asked to report early life exposures including whether they were born 2 or more weeks premature. When self-reports of preterm birth were compared to similar data collected from a sample of mothers of the participants, approximately 90% agreement was found[11].

Breastfeeding. In the 1991 NHSII and 1992 NHS questionnaires, participants were also asked whether they had been breastfed (response categories: no/yes/not sure) and for how long (response categories: no/ 3 months/4–8 months/ 9 months/not sure). Participants who were not sure if they were breastfed did not answer the duration question; therefore those uncertain of their duration of being breastfed were among those responding "yes" to the first breastfeeding question. In a sample of NHSII participants, Troy and colleagues validated self-report of being breastfed against mother's report with 82% sensitivity and 86% specificity[12]. The correlation between mother's and daughter's reports of breastfeeding duration was 0.74[12].

Incident rheumatoid arthritis. On each biennial followup questionnaire, participants were asked about a variety of doctor-diagnosed health conditions. Those reporting any systemic rheumatic disease were asked to complete a previously validated Connective Tissue Disease Screening Questionnaire (CSQ), which had demonstrated 85% sensitivity for RA[13], and for permission to review their medical records. The medical records of participants who screened positively for the signs and symptoms of both typical and atypical connective tissue diseases were evaluated independently by 2 rheumatologists, blinded to perinatal exposures, with disagreements resolved by consensus. The presence of at least 4 of 7 American College of Rheumatology criteria documented in the medical record constituted confirmed RA[14]. A total of 913 incident RA cases were confirmed during followup: 727 NHS participants through May 31, 2004, and 186 NHSII participants followed through May 31, 2003.

In secondary analyses we also studied whether the associations between perinatal exposures and RA were similar for those subjects who were documented to be RF-positive and those who were RF-negative[15].

Additional covariates. In NHS, data were available on the following potential confounders and effect modifiers: parents' occupation (as a proxy for childhood socioeconomic status), maternal history of diabetes (as a proxy for gestational diabetes), childhood exposure to cigarette smoke (as a proxy for smoke exposure *in utero*), race/ethnicity, and birth weight. In NHSII similar data were available except that parents' occupation was not collected, and passive exposure to smoke *in utero* was ascertained explicitly.

Statistical analysis. Cohort characteristics were summarized using descriptive statistics stratified by breastfeeding exposure and preterm birth status. We estimated hazard ratios as a measure of relative risk (RR) of incident RA using age-stratified Cox proportional hazards models and multivariable Cox models adjusted for the following covariates: race, parents' occupations, early life exposure to passive cigarette smoke, and birth weight. These covariates were adjusted for as potential confounding factors because they satisfied the criteria for confounding and were believed to be confounders *a priori*. Specifically. they were associated with the perinatal-exposure independent risk factors of RA, and not the hypothesized causal pathway between perinatal exposure and RA. The proportional hazards assumption was evaluated using the Wald test to assess the significance of the interaction between time and each perinatal exposure[16]. In the primary analysis, among subjects free of RA at baseline (1976 in NHS or 1989 in NHSII), participants were followed from return of the baseline questionnaire until date of diagnosis of confirmed incident RA, date of death, or until the return of their last questionnaire. Random-effects meta-analysis methods were used to combine data from the 2 cohorts to account for possible heterogeneity in the effect of exposure across the 2 cohorts[17].

Statistical interaction terms were used to test for effect modification by a number of factors. We examined effect modification by maternal smoking during childhood to account for the possibility of cigarette smoke altering the composition, biological effects, or metabolism of breast milk. We examined effect modification by maternal diabetes history (considered as a proxy for gestational diabetes). In gestational diabetes the fetal environment may affect perinatal factors such as birth weight and intrauterine growth. And lastly we assessed effect modification by preterm birth status, since a preterm infant's immune system is less developed and may function differently with regard to tolerance and antigen-processing during breastfeeding.

Perinatal exposure data were obtained years after enrollment in both cohorts, raising the possibility that RA diagnosed before perinatal factors were assessed might lead to differential recall of perinatal exposures. We therefore performed sensitivity analyses restricting followup to a prospective period after perinatal exposure data were collected to consider the possible role of such recall bias. We conducted an additional secondary analysis in the NHS cohort to consider possible selection bias related to excluding prevalent RA at baseline.

RESULTS

We confirmed 913 incident cases of RA in our study population during followup. The average age at diagnosis was 58 in NHS and 45 in NHSII. Thirty percent of NHS and 25% of NHSII participants with RA had radiographic changes consistent with erosive disease, and 59% were RF-positive at diagnosis in both cohorts. Being born preterm was associated with early-life cigarette smoke exposure and low birth weight in these data (Table 1). Women who were breastfed in their infancy were less likely to have parents who smoked and were less likely to have low birth weight (Table 2).

Preterm birth. Preterm birth was not associated with RA incidence in either cohort. The combined relative risk was 1.1 (95% CI 0.8, 1.5) in multivariable adjusted models (Table 3). Results were comparable for RF-positive and RF-negative RA (Table 4). There appeared to be no interaction by maternal smoking or maternal diabetes (data not shown).

Table 1. Study population characteristics in both cohorts stratified by self-reported preterm birth status. Data presented as means (SD) or percentage, unless noted otherwise.

	NHS Preterm Birth		NHSII Preterm Birth	
	Yes	No	Yes	No
Participants, n (%)	3588 (4.2)	82,727 (95.8)	7104 (7.2)	91,027 (92.8)
Age at baseline, yrs	42 (7.1)	43 (7.1)	34 (4.7)	34 (4.7)
Pregnant mother smoked*	NA	NA	27.9	20.4
Mother smoked in home**	24.3	20.1	36.0	30.0
Father smoked in home**	57.0	54.7	49.6	47.5
BMI at age 18 yrs	18.7 (7.4)	19.0 (7.2)	21.3 (3.5)	21.3 (3.3)
BMI at baseline	23.5 (4.7)	23.5 (4.5)	24.3 (5.4)	24.1 (5.0)
Maternal diabetes	9.9	9.8	7.9	7.1
Low birth weight, < 5.5 lbs†	70.6	5.4	49.2	3.4
High birth weight, > 10 lbs†	0.2	2.0	0.1	1.3
African American	0.8	1.3	1.2	1.6
Hispanic	0.7	0.6	1.3	1.5
Current smoker at baseline	30.0	30.7	13.3	13.0
Past smoker at baseline	23.5	24.6	19.1	21.6

* Asked in 1999 NHSII only. ** Asked 1982 in NHS, 1999 in NHSII. † Asked in 1992 in NHS, 1991 in NHSII. NHS: Nurses' Health Study; BMI: body mass index; NA: not available.

Table 2. Nurses' Health Study Study (NHS) population characteristics at baseline stratified by breastfeeding exposure. Data presented as means (SD) or percentages unless noted otherwise.

	NHS Breastfed in Infancy***		NHSII Breastfed in Infancy***	
	Yes	No	Yes	No
Participants, n (%)	46,627 (53.8)	25,410 (29.3)	31,214 (31.8)	59,672 (60.8)
Age at baseline, yrs	44 (6.9)	40 (6.8)	35 (4.7)	34 (4.6)
Pregnant mother smoked*	NA	NA	16.8	23.5
Mother smoked in home**	17.0	25.2	24.9	33.4
Father smoked in home**	53.7	56.9	43.8	49.7
BMI at age 18 yrs	19.1 (7.1)	18.9 (7.3)	21.2 (3.2)	21.3 (3.4)
BMI at baseline	23.6 (4.6)	23.2 (4.5)	24.1 (5.0)	24.1 (5.0)
Maternal diabetes	10.4	8.9	6.9	7.2
Low birth weight, < 5.5 lb†	6.5	11.9	4.4	8.0
High birth weight, > 10 lbs†	2.3	1.5	1.3	1.1
Father professional/managerial job††	24.3	28.4	NA	NA
Mother professional/managerial job††	8.3	9.6	NA	NA
African American	1.6	0.70	2.0	1.2
Hispanic	0.78	0.44	2.2	1.0
Current smoker at baseline	8.2	9.2	11.3	13.8
Past smoker at baseline	42.8	46.2	20.0	22.2

* Asked in 1999 NHSII only. ** Asked 1982 in NHS, 1999 in NHSII. † Asked 1992 in NHS, 1991 in NHSII. †† Asked only in NHS. *** Remaining participants either reported uncertain breastfeeding or skipped the question. BMI: body mass index; NA: not available.

Breastfeeding. Being breastfed was not associated with RA in either cohort. The combined relative risk was 1.0 (95% CI 0.7, 1.4; Table 3). The combined RR of RA for 3 months or less of being breastfed versus no breastfeeding was 0.8 (95% CI 0.6, 1.1; Table 3). There appeared to be no effect modification by maternal smoking, maternal diabetes, or preterm status (data not shown). Estimates were essentially unchanged when we considered RF-positive RA as a secondary outcome (Table 4). In the NHS cohort being breastfed was associated with a reduced rate of RF-negative RA

(RR = 0.7, 95% CI 0.5, 0.9). None of the breastfeeding duration categories appeared to be significantly associated with RA (all, RF-positive, and RF-negative), with the exception of long duration of breastfeeding (9 mo) protecting against RF-negative RA in the NHS cohort (RR = 0.6, 95% CI 0.4, 0.9).

Sensitivity analysis. When followup was restricted to the periods after exposure ascertainment (prospective analysis), results were similar in both NHS and NHSII. Additionally, we found nearly identical results when 19 confirmed preva-

Table 3. Estimated hazard ratios (95% CI) of the association between perinatal factors and incident rheumatoid arthritis (RA).

| | Nurses' Health Study | | | Nurses' Health Study II | | | Combined |
	No. RA	Univariate	Multivariable-Adj	No. RA	Univariate	Multivariable-Adj	Multivariable-Adj
Preterm birth*							
No	696	1.0 (ref)	1.0 (ref)	172	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	31	1.1 (0.7, 1.5)	1.1 (0.7, 1.5)	14	1.1 (0.6, 1.8)	1.0 (0.6, 1.8)	1.1 (0.8, 1.5)
Breastfed†							
No	230	1.0 (ref)	1.0 (ref)	105	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	375	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	68	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.0 (0.7, 1.4)
Unknown	122	0.8 (0.7, 1.1)	0.9 (0.7, 1.1)	10	0.9 (0.5, 1.8)	1.0 (0.5, 1.9)	0.9 (0.7, 1.1)
Duration breastfed†							
None	230	1.0 (ref)	1.0 (ref)	105	1.0 (ref)	1.0 (ref)	1.0 (ref)
3 mo	29	0.7 (0.5, 1.1)	0.7 (0.5, 1.1)	16	0.9 (0.5, 1.5)	0.9 (0.5, 1.5)	0.8 (0.6, 1.1)
4–8 mo	60	1.0 (0.7, 1.3)	0.9 (0.7, 1.2)	19	1.3 (0.8, 2.1)	1.3 (0.8, 2.2)	1.0 (0.7, 1.4)
9 mo	66	0.7 (0.6, 1.0)	0.7 (0.6, 1.0)	13	1.9 (1.1, 3.4)	2.0 (1.1, 3.6)	1.1 (0.4, 3.2)
Unknown	220	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	20	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)	0.9 (0.7, 1.1)

* Multivariable preterm birth models adjusted for age, parents' occupations (NHS only), race/ethnicity, mother smoked in childhood, father smoked in childhood, fetal exposure to cigarette smoke (NHSII only). † Breastfeeding exposure models adjusted for parents' occupations (NHS only), race/ethnicity, age mother smoked in childhood, father smoked in childhood, fetal exposure to cigarette smoke (NHSII only), birth weight, and preterm status. Multivariable-adj: multivariable adjusted.

Table 4. Estimated multivariable-adjusted hazard ratios (95% CI) of the association between perinatal factors and incident rheumatoid arthritis (RA) further classified by rheumatoid factor (RF) seropositivity.

| | Nurses' Health Study | | Nurses' Health Study II | | Combined | |
	RF+	RF–	RF+	RF–	RF+	RF–
Preterm birth*						
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.0 (0.6, 1.6)	1.1 (0.7, 2.0)	0.8 (0.3, 1.7)	1.5 (0.7, 3.2)	0.9 (0.6, 1.5)	1.2 (0.8, 1.9)
Breastfed†						
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.9 (0.7, 1.1)	0.7 (0.5, 0.9)	1.2 (0.8, 1.8)	1.2 (0.7, 1.9)	1.0 (0.8, 1.3)	0.9 (0.5, 1.5)
Unknown	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	0.5 (0.2, 1.6)	1.6 (0.7, 3.6)	0.8 (0.6, 1.2)	1.1 (0.6, 1.8)
Duration breastfed†						
None	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
3 mo	0.8 (0.5, 1.3)	0.7 (0.4, 1.3)	0.8 (0.4, 1.6)	1.1 (0.5, 2.4)	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)
4–8 mo	1.0 (0.7, 1.4)	0.9 (0.6, 1.4)	1.4 (0.8, 2.7)	1.2 (0.5, 2.6)	1.1 (0.8, 1.5)	1.0 (0.7, 1.4)
9 mo	0.9 (0.6, 1.2)	0.6 (0.4, 0.9)	1.9 (0.9, 4.2)	2.2 (0.9, 5.2)	1.2 (0.6, 2.5)	1.1 (0.3, 3.8)
Unknown	0.9 (0.7, 1.2)	0.7 (0.5, 1.0)	1.3 (0.7, 2.4)	0.9 (0.4, 2.1)	1.0 (0.7, 1.3)	0.7 (0.5, 1.0)

* Multivariable preterm birth models adjusted for parents' occupations (NHS only), race/ethnicity, mother smoked in childhood, father smoked in childhood, fetal exposure to cigarette smoke (NHSII only), and stratified by age and study time. † Breastfeeding exposure models adjusted for parents' occupations (NHS only), race/ethnicity, age mother smoked in childhood, father smoked in childhood, fetal exposure to cigarette smoke (NHSII only), birth weight, preterm status, and stratified by age and study time.

lent RA cases were included as cases in the NHS study population (data not shown).

DISCUSSION

We found no statistically significant association between either preterm birth or being breastfed with the onset of RA. To our knowledge the only other study assessing the relationship between the perinatal characteristics of being breastfed and preterm birth and RA is the population-based case-control study by Jacobsson and colleagues[4]. Using birth records and a disease register in Malmo, Sweden, the investigators identified 77 RA cases (67 cases included in the multivariable analysis) and 308 population-based con-

trols. Records were used to classify their participants' perinatal characteristics, where data for a number of the perinatal factors were recorded at time of delivery, minimizing the possibility of recall bias. Having breastfeeding initiated in the hospital was associated with a striking 80% to 90% reduction in odds of RA. In contrast, using data from 2 large prospective cohorts, with over 10 times the number of cases, we found no association between being breastfed and RA incidence. However, comparing results from Jacobsson, *et al* to NHS results for another perinatal exposure, birth weight, demonstrated similar results[4,6].

Study design, exposure assessment, and other analytic considerations may explain the disparate findings for breast

feeding exposure. NHS and NHSII participants are predominantly American women, while Jacobsson's study population[4] included Swedish men and women. By design, Jacobsson's study identified both early and late adult-onset RA, whereas our participants were women free of RA at enrollment between the ages of 25 and 55 years. The median age at diagnosis was 46 years in their study, similar to that in the NHSII cohort (median age 45 yrs). Nearly 80% of the cases in our study, however, came from the NHS, where the median age at diagnosis was 58 years. The Swedish study used data from a local register of patients seen as outpatients either at Malmö University Hospital or one of 3 private rheumatologists in the city. RA cases in Jacobsson's study might have had more severe RA — 76% were RF-positive and 85% had erosions, compared with 59% RF-positive and 29% with erosions at RA diagnosis in our study. However, the Swedish cases included prevalent RA, which might be associated with longer disease duration and more radiographic findings. When we restricted our case definition to include only RF-positive RA, our results were relatively unchanged. When we defined our outcome as RF-negative RA, we found that being breastfed and for longer duration may be protective against developing RF-negative RA among the older cohort of NHS participants. One might expect that if we were to find an association it would be for the RF-positive outcome because the previous study[4], which found a strong protective effect, had over 75% RF-positive RA. Further, the exposures assessed in these 2 studies differ. The Jacobsson study[4] does not explicitly examine duration of breastfeeding, which our study does. If the protective effect were from immune-modulating effects of prolonged exposure to maternal immunoglobulins, hormones, cytokines, and numerous antigens[18,19], then prolonged exposure to breast milk would be likely to be relevant etiologically. However, if first exposure is more important, then breastfeeding initiation identifies that risk factor better. On the other hand, we would expect to observe an association in our data, if one were present, among the ever-breastfed category, which we find in only one of the cohorts for our secondary outcome of RF-negative RA.

Some limitations and strengths of our study must be considered. The study population was restricted to adult women in the US not diagnosed with RA at enrollment (age range 25–55 yrs at enrollment), limiting our generalizability to adult-onset RA after age 25 in women. Being breastfed was protective in some[4,20] but not all studies[21,22] for juvenile-onset RA. If being breastfed does protect against the development of RA in childhood or early adulthood, then women who were not breastfed and more likely to have developed RA may be underrepresented in our study either because they did not go on to become nurses or they were less likely to participate in the Nurses' Health Studies because of prevalent RA at baseline. When 19 confirmed prevalent RA cases satisfying the multiple exclusion criteria in NHS were included in the analysis we found that the results were essentially unchanged. When roughly 250 additional prevalent self-reports were included in the NHS study population, results were comparable, although centered closer to the null and with wider confidence intervals.

Although validation studies suggest that these self-reported perinatal exposures are valid, we cannot exclude the possibility of exposure misclassification. The validation study by Troy and colleagues[12] did not consider the older NHS population, which may not be reported with the same accuracy as the younger NHSII sample. Further, the mother's self-report may not be the ideal "gold standard." Imperfect reporting of breastfeeding exposure and its duration may also have led to some exposure misclassification. This is likely to be nondifferential, but the direction of potential bias is difficult to predict as most perinatal characteristics in our study had at least 3 categories, i.e., yes/no/don't know. Missing or uncertain perinatal exposures were considered as their own category of exposure. Although not shown in Tables 1 and 2, there appeared to be little difference in cohort characteristics among those with missing and non-missing exposure data. Additionally, it is possible that the women who were not breastfed were exposed to different infant feeding alternatives, cow's milk versus soy-based formulas, for instance, and the available data do not adequately characterize this. Preterm birth was defined using participants' identification of being born at least 2 weeks preterm, as worded on the questionnaires. This definition does not conform to the definition of preterm birth currently recommended by the American College of Obstetrics and Gynecology of at least 3 weeks preterm; therefore we were unable to consider moderate versus severe prematurity as a risk factor. We also cannot exclude the possibility of misclassification of RA diagnosis, but there is no reason to believe that this would differ by perinatal characteristics. When we used RF seropositivity to define subtypes of RA, we found that being breastfed and for a longer duration may be associated with a lower rate of RF-negative RA. We cannot exclude the possibility that this is a false-positive finding because of the number of outcomes and exposures we considered in our study; however, the effect estimate was relatively modest and statistically significant despite decreased power.

Our analysis is based on observational data and therefore we cannot exclude the possibility that there remains bias due to confounding by measured or unmeasured factors. For instance, the type of breast milk alternative available in the US has had secular changes, but other unmeasured confounders could have changed over time as well. Breastfeeding practices in the US changed with time and are, in part, related to social factors that we cannot adequately adjust for due to limited data on socioeconomic factors during the nurse-participant's infancy and childhood. However, adjustment for available potential confounders

did not appreciably change the estimated associations for any of the perinatal factors we considered. We cannot exclude the possibility that heterogeneity of the association between breastfeeding and incident RA in women exists in relation to the 2 cohorts, which represent 2 distinct birth cohorts.

We found that neither preterm birth nor being breastfed was significantly associated with incidence of RA. In a well powered study with over 900 confirmed incident cases of RA, we showed findings consistent with previous investigations for a null association between RA and gestational age, but were unable to confirm the previously reported protective effect of being breastfed.

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