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Early Life Factors and Risk of Inflammatory Bowel Disease in Adulthood

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Abstract

Background—Early life factors have been postulated to play a role in development of immune tolerance and intestinal microbiome, which in turn may influence the risk of inflammatory bowel disease.

Methods—We conducted a prospective cohort study of 60,186 U.S. women enrolled since 1976 in the Nurses Health Study I (NHS I) and 86,495 women enrolled since 1989 in the Nurses' Health Study II (NHS II) with no prior history of ulcerative colitis (UC) or Crohn's disease (CD). Information about breastfeeding, birthweight, and preterm birth were collected in 1992 in NHS I and 1991 in NHS II. Diagnoses of CD and UC were confirmed through review of medical records. We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results—Among 146,681 women over 3,373,726 person-years of follow-up, we documented 248 cases of CD and 304 cases of UC through 2007 in NHSII and 2008 in NHSI. The median age of diagnosis was 51 for CD and 49 for UC. Compared to women who were not breastfed, women who were breastfed had multivariate-adjusted HRs of 0.99 (95% CI, 0.76–1.30) for CD and 1.03 (95% CI, 0.81–1.32) for UC. Similarly, low or high birthweight, and preterm birth were not significantly associated with risk of UC or CD.

Conclusion—In two large prospective cohorts of US women, we did not observe a significant association between early life factors including having been breastfed, birthweight, preterm birth, and risk of adult onset UC and CD.

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Authors Contributions

HK - study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis.
ANA- acquisition of data; critical revision of the manuscript.
LMH - acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.
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Keywords

Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Early Life Factors; Breastfeeding; Birthweight; Prematurity; and Nurses' Health Study

INTRODUCTION

The key pathogenic mechanism underlying inflammatory bowel disease (IBD) is an inappropriate immune response to the intestinal microbiome or loss of tolerance in a genetically susceptible host.[1] Previous epidemiologic studies have shown that a number of early life factors posited to influence development of immune tolerance, including breastfeeding and birthweight, may be potential risk factors for development of adult onset autoimmune diseases. [2–5] In addition, recent studies have illustrated the impact of early life factors in defining the composition of intestinal microbiome.[6–8] Although the exact role of the intestinal microbiome in the pathogenesis of IBD remains poorly defined, its composition in genetically predisposed patients may influence the risk of development of IBD.

Limited epidemiological data suggest a link between having been breastfed and risk of developing IBD.[9] However, many of these studies lack information on duration of having been breastfed or failed to confirm diagnoses of IBD through rigorous medical record review. [10–12] In addition, a number of these studies were underpowered leading to inconclusive results. [13,14] One previous study found an association between preterm birth and incident IBD but neither the exposure information nor the diagnoses were validated. [15] We therefore sought to examine the association between early life factors, including having been breastfed, preterm birth, and birthweight, and risk of incident UC and CD during adulthood in two large prospective cohorts of US women, the Nurses Health Study I and II (NHS I and II), in which validated information about early life factors were collected. These cohorts offered us a unique opportunity to examine early life factors in the context of important lifestyle risk factors that may either confound or modify its association with UC and CD.

METHODS

Study Population

The NHS I is a prospective cohort that began in 1976 when 121,700 U.S. female registered nurses, ages 30 to 55 years, completed a mailed health questionnaire. Follow up questionnaires are mailed every two years to update health information. In 1989, a parallel cohort, the NHS II, enrolled 116,686 U.S. female nurses between the ages of 25–42 years. These women have been followed with similar biennial questionnaires. Follow-up for the current study exceeded 90%. The institutional review board at the Brigham and Women's Hospital approved this study.

Assessment of Early Life Factors

In the 1991 NHS II and 1992 NHS I questionnaires, participants were 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). In a subsample of NHS II participants, Troy and colleagues validated the self-report of being breastfed against mother's report with 82% sensitivity and 86% specificity.[16] The correlation between mother's and daughter's reports of breastfeeding duration was 0.74.

In the 1991 NHS II and 1992 NHS I questionnaires, participants were asked to report 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, 90% agreement was found.[17]

In the 1991 NHS II questionnaire and in the 1992 NHS I questionnaire, women were asked to report their own birth weight in categories (<2.26 kg; 2.3–2.49 kg; 2.5–3.175 kg; 3.2–3.85 kg; 3.9–4.54 kg; >4.54 kg). In a validation study in NHS II, birth weight was obtained from state birth certificates for 220 randomly chosen female nurses from the NHS II, and divided into five categories. Actual birth weight was then compared with self-reported birth weight. Seventy percent of nurses reported the same birth weight category as documented on their birth certificate. Overall, the spearman correlation coefficient was 0.74, demonstrating substantial correlation. [16]

We limited our analysis to individuals who provided information on early life factors on the 1991 NHSII and 1992 NHSI questionnaires. The baseline characteristics of individuals who did not provide such information was similar to participants who provided information on early life factors (for NHS, mean age: 41.9 vs 43.6, mean BMI: 23.4 vs 23.6, ever smoking: 55% vs. 56%; for NHS II, mean age: 34.7 vs. 35.0, mean BMI: 24.1 vs. 24.1, ever smoking: 34% vs. 36%). Similarly, the incidence of CD and UC during follow up were similar in both groups.

Covariate Information

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. Information on cigarette smoking, weight, and use of oral contraceptives were collected every 2 years. Body mass index (BMI) was computed using weight in kilograms divided by height in square meters as reported at baseline. Participants' self-report of body weight, height, and use of oral contraceptives has been previously validated.[18,19] Data on maternal history of smoking during pregnancy were also collected in both cohorts. We did not specifically collect information about gestational diabetes; however, we did use data on history of diabetes in the participant's mother in our multivariate models.

Outcome Ascertainment

We have previously detailed our methods for confirming cases of CD and UC.[20] In brief, since 1976 in NHS I and 1989 in NHS II, participants have reported diagnoses of UC or CD through an open-ended response on biennial surveys. In NHS I, we have specifically queried participants about diagnoses of UC since 1982 and CD since 1992. In NHS II, we have specifically queried participants about diagnoses of both UC and CD since 1993. When a diagnosis was reported on any biennial questionnaire, a supplementary questionnaire and related medical records were requested and reviewed by two gastroenterologists blinded to exposure information. We excluded participants who subsequently denied the diagnosis on the supplementary questionnaire or permission to review their records. Data were extracted on diagnostic tests, histopathology, anatomic location of disease, and disease behavior. Using standardized criteria, [21–24] UC diagnosis was based on a typical clinical presentation ≥ 4 weeks and endoscopic or surgical pathological specimen consistent with UC (e.g. evidence of chronicity). CD diagnosis was based on a typical clinical history for ≥4 weeks and endoscopy or radiologic evaluation demonstrating small bowel findings, or surgical findings consistent with CD combined with pathology suggesting transmural inflammation or granuloma contributed to a diagnosis of CD. Disagreements were resolved through consensus. Among those women whom we received adequate medical records, the case confirmation rate for IBD was 78% in NHS and 74% in NHS II.[20]

Statistical Analysis

Person-time for each participant was calculated from the date of return of baseline questionnaire to the date of the diagnosis of UC or CD, date of last questionnaire, death from any cause, or June 1, 2008 for NHS I and June 1, 2007 for NHS II, whichever came first. We used Cox proportional hazards modeling with time-varying covariates to adjust for other known or suspected risk factors prior to each 2-year interval to calculate adjusted hazard ratios (HR) and 95% confidence interval (CIs). Because weight may be influenced by preclinical disease, we adjusted for BMI using the baseline value, consistent with prior analyses.[25] We observed no heterogeneity in the association of any of the specified early life factors with CD or UC in separate analyses of NHSI and NHSII (all P for heterogeneity >0.50 for both UC and CD). Thus, we pooled individual-level data from NHSI and NHSII and adjusted for cohort membership in all analyses. We also examined the association between early life factors and risk of UC or CD according to strata of history of diabetes in the mother and maternal smoking during pregnancy and evaluated for potential interaction using cross-classified categories of these risk factors and early life factors. We tested the significance of interactions by using the log likelihood ratio test comparing the model with cross-classified categories with a model that included these factors as independent variables. We used SAS version 9.1.3 (Cary, NC) for these analyses. All *P*-values were 2-sided and < 0.05 was considered statistically significant.

RESULTS

Among 146,681 women (60,186 in NHS I and 86,495 in NHS II) who provided information on early life factors, we documented 248 incident cases of CD and 304 incident cases of UC through 2007 in NHS II and 2008 in NHS I over 3,373,726 total person-years of follow up. The baseline characteristics according to whether they were breastfed in early life are shown in Table 1. Compared to women who were not breastfed, women who were breastfed were older, less likely to be born preterm, had low birthweight, had a mother who smoked during pregnancy, or used oral contraceptives.

Breastfeeding

We did not observe a significant association between having been breastfed and risk of UC or CD (Table 2). Compared to women who were not breastfed, women who were breastfed had an age-adjusted HR of 0.99 (95% CI, 0.76–1.29) for CD and 1.03 (95% CI, 0.81–1.31) for UC. These estimates were not significantly altered after adjusting for potential confounders including smoking, BMI, birthweight, preterm birth, history of diabetes in the mother, maternal history of smoking during pregnancy, and oral contraceptive use. The multivariate-adjusted HRs were 0.99 (95% CI, 0.76–1.30) for CD and 1.03 (95% CI, 0.81–1.32) for UC. We also evaluated the effect of duration of being breastfed on subsequent risk of UC and CD (Table 3). Compared to women who were not breastfed, the multivariate-adjusted HR of CD was 1.26 (95% CI, 0.83–1.93) for women who were breastfed for ≤ 3 months, 0.94 (95% CI, 0.66–1.32) for women who were breastfed for 4–8 months, and 1.02 (95%CI, 0.63–1.66) for women who were breastfed for ≥ 9 months. Similarly for UC, the multivariate-adjusted HR was 1.09 (95% CI, 0.73–1.72) for women who were breastfed for ≤ 3 months, 0.97 (95% CI, 0.65–1.46) for women who were breastfed for 4–8 months, and 0.90 (0.56–1.46) for women who were breastfed for ≥ 9 months.

Preterm Birth and Birthweight

Similar to breastfeeding, we did not observe a statistically significant association between having been born preterm and risk of UC or CD (Table 4). The multivariate-adjusted HRs were 0.69 (95% CI, 0.37–1.29) for CD and 0.82 (95% CI, 0.46–1.43) for UC. We also evaluated the association between birth weight and risk of UC and CD (Table 5). Compared

to women with normal birthweight, women with low birthweight had a multivariate-adjusted HR of 1.29 (95% CI, 0.79–2.11) for CD and 0.91 (95% CI, 0.55–1.49) for UC. Similarly, women with high birthweight (> 4.54 kg) did not have an increased risk of developing UC or CD. The multivariate-adjusted HRs were 1.06 (95% CI, 0.71–1.58) for CD and 1.02 (95% CI, 0.71–1.47) for UC.

We considered the possibility that history of diabetes in the mother or smoking during pregnancy may modify the effect of these early life factors on risk of UC and CD in stratified analyses according to these potential effect modifiers. The effect of breastfeeding, preterm birth, or birthweight on risk of UC or CD did not appear to be significantly different within any strata according to history of diabetes in the mother or smoking during pregnancy (all $P_{interaction} > 0.10$). We also assessed whether these potential effect modifiers are independently associated with risk of UC or CD. Although maternal smoking during pregnancy was not associated with risk of UC or CD, history of diabetes in the mother was associated with an increased risk of CD (multivariate-adjusted HR = 1.64, 95% CI 1.15–2.33) but not UC (**Supplementary Material)**.

Because a diagnosis of UC or CD could influence recall of early life factors, we performed sensitivity analyses limiting our follow up to the time period after the first exposure ascertainment (1991 in NHS II and 1992 in NHS I). Compared to women who were not breastfed, women who were breastfed had a multivariate-adjusted HRs of 0.93 (95% CI, 0.69–1.27) for CD and 1.04 (95% CI, 0.79–1.36). Similarly, in these sensitivity analyses, there was no association between preterm birth or birthweight and risk of UC or CD (data not shown).

DISCUSSION

The composition of an infant's intestinal flora is determined through exposure to bacteria from the mother as well as the environment. Although the exact role of intestinal microbiome in the pathogenesis of IBD remains poorly defined, its specific make up and/or alteration in its composition in genetically predisposed patients may influence the risk of development of IBD. Studies have shown distinct patterns of microbial consortium in gastrointestinal tracts of preterm birth [8], extremely low birthweight [7], and infants who have been breastfed[26]. Taken together these findings may suggest a plausible biologic mechanism linking events in early life to development of later onset IBD. However, in two large prospective cohorts of US women, we did not observe an association between having been breastfed, preterm birth, birthweight and risk of UC and CD. We did observe an association between history of diabetes in the mother and risk of CD. However, it is unclear whether gestational diabetes is a early life factor that also may be associated with CD; future studies are needed to investigate the association between gestational diabetes and risk of CD or UC in their offspring.

A systematic review and meta-analysis of previous studies observed that breastfeeding is associated with a lower risk of both UC and CD.[9] Our results may contrast with these findings since we examined risk of incident CD and UC in adulthood (after age 39) whereas the majority of the studies included in prior meta-analyses were comprised of pediatric or childhood IBD cases. [27–33] Genome-wide studies[34,35] have shown that genetic susceptibility loci for IBD are largely consistent according to age of diagnosis. However, cases of IBD diagnosed in childhood or adolescence have distinct phenotypic features and natural history compared to cases of IBD diagnosed in adulthood, suggesting the likelihood of divergent environmental risk factors that may influence risk of early-onset IBD compared with adult-onset IBD. Alternatively, it is possible that the impact of early life factors on disease pathogenesis in a genetically susceptible individual may become apparent only within

childhood or adolescence, which would dilute the ability to detect associations with incident disease diagnosed in adulthood.

Our study has several notable strengths. First, our prospective study design avoids the potential recall and selection biases of retrospective, case-control studies which collect data on diet and lifestyle after diagnosis of CD or UC. Second, we confirmed all cases of CD and UC through medical record review, a significant advantage over studies that rely on self-report or discharge codes, which may not accurately reflect true diagnoses. Third, the availability of detailed and validated information on BMI, prior oral contraceptive use, smoking, and other important early life factors allowed us to control for a number of potential confounding factors that may have influenced our observed associations. Fourth, we used validated data on early life factors.

We acknowledge several limitations. First, our cohorts, which consist of female health professionals, may not be representative of the overall US population. However, as we have previously reported, [20] our age-specific incidence of CD and UC are largely similar to rates from other U.S. populations. In addition, previous studies have shown that the prevalence of risk factors, such as smoking and BMI, in our cohort is consistent with those of the broader population of U.S. women.[36,37] Second, although validation studies have demonstrated that data on early life factors reported by these health professionals are highly accurate, we cannot exclude the possibility of exposure misclassification. Inaccurate reporting of breastfeeding duration or birthweight could have biased our study against finding significant associations. Third, our definition of preterm birth in our questionnaires was delivery 2 or more weeks preterm. However, others define preterm birth as delivery 3 or more weeks preterm.[38] Thus, it is possible that alternative definitions of preterm birth, representing more significant prematurity, may be associated with risk. Fourth, the number of cases in some of our exposure categories were relatively small, limiting the precision of our risk estimates. Moreover, we are unable to exclude the possibility of a more modest association between these early life factors and risk of adult-onset IBD. Finally, we do not have detailed information about other potential early life factors, including mode of delivery and early exposure to antibiotics, which may also influence risk of IBD.

In conclusion, in two large prospective cohorts of US women, we did not find a significant association between early life factors including having been breastfed, preterm birth, birthweight and risk of UC and CD in adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline Characteristics of Participants According to Breastfeeding Status*

	Yes N = 67,062	No N = 76,619
Age, mean (SD)	39.8 (7.3)	35.9 (5.7)
Race (non-white), %§	4	3
Smoking, %		
Never	58	57
Past	22	23
Current	20	20
Body mass index (kg/m^2), %		
< 20	15	15
20–24.9	57	56
25–29.9	19	19
≥30	9	10
Ever us of oral contraceptives, %	69	72
Mother smoked during pregnancy, %†	13	19
History of diabetes in the mother, %§	10	9
Preterm birth, %	5	9
Birthweight (kg), %		
< 2.26	7	12
2.3–3.175	30	32
3.2–4.54	49	45
> 4.54	15	11

Abbreviations: standard deviation (SD)

*Breastfeeding status refers to if participant was breast fed in early life. Baseline characteristics on age, body-mass index, and oral contraceptives according to the 1976 questionnaire in NHS I and1989 questionnaire in NHS II. Race, history of diabetes in the mother, and maternal smoking during pregnancy were based on the 1991 questionnaire in NHS II and 1992 questionnaire in NHS I. Values are standardized to the age distribution of the study population.

†Asked in 2004 in NHS and 1993 in NHS II questionnaires.

§Asked in 1992 in NHS and 1991 in NHS II questionnaires.

Table 2

Risk of Crohn's Disease and Ulcerative Colitis According to Breastfeeding Status *

	No	Yes
Person-Years	1,697,462	1,676,264
Crohn's Disease		
Cases	128	120
Age-Adjusted Incidence§	8	7
Age-Adjusted, 95% CI	1.00	0.99 (0.76–1.29)
MV-Adjusted, 95% CI†	1.00	1.00 (0.76–1.30)
Ulcerative Colitis		
Cases	159	145
Age-Adjusted Incidence§	9	9
Age-Adjusted, 95% CI	1.00	1.03 (0.81–1.31)
MV-Adjusted, 95% CI†	1.00	1.03 (0.81–1.31)

Abbreviations: confidence interval (CI), multivariate (MV)

*Breastfeeding is defined as being breastfed.

§Reported as number of cases per 100,000 person-years.

†Adjusted for age (months), cohort (NHSI vs. NHSII), BMI (<20, 20–24,9, 25–29.9, ≥ 30 kg/m^2), smoking (never, past, current), history of diabetes in the mother (yes, no), maternal smoking during pregnancy (yes, no, unknown), ever use of oral contraceptives (yes, no), prematurity (yes, no), and birthweight (< 2.26, 2.3–3.175, 3.2–4.54, > 4.54 kg).

Table 3

Risk of Crohn's Disease and Ulcerative Colitis According to Duration of Breastfeeding*

	Breastfeeding Duration (months)				
	0	**≤ 3**	**4–8**	**≥ 9**	**P_{trend}**
Person-Years	1,697,462	288,330	329,579	289,331	
Crohn's Disease					
Cases	128	26	22	22	
Age-Adjusted Incidence§	8	9	7	8	
Age-Adjusted, 95% CI	1.00	1.25 (0.82–1.91)	0.92 (0.58–1.45)	1.03 (0.64–1.65)	0.51
MV-Adjusted, 95% CI†	1.00	1.26 (0.83–1.93)	0.92 (0.58–1.46)	1.03 (0.64–1.65)	0.52
Ulcerative Colitis					
Cases	159	29	29	22	
Age-Adjusted Incidence§	9	10	9	8	
Age-Adjusted, 95% CI	1.00	1.10 (0.74–1.63)	0.99 (0.66–1.48)	0.92 (0.58–1.46)	0.88
MV-Adjusted, 95% CI†	1.00	1.09 (0.73–1.62)	0.99 (0.66–1.48)	0.93 (0.58–1.49)	0.82

Abbreviations: confidence interval (CI), multivariate (MV)

*Breastfeeding defined as the number of months being breastfed. 28,674 participants were not sure of the duration they were breastfed (this included 50 CD and 65 UC women)

§Reported as number of cases per 100,000 person-years.

†Adjusted for age (months), cohort (NHSI vs. NHSII), BMI (<20, 20–24,9, 25–29.9, ≥ 30 kg/m^2), smoking (never, past, current), history of diabetes in the mother (yes, no), maternal smoking during pregnancy (yes, no, unknown), ever use of oral contraceptives (yes, no), prematurity (yes, no), and birthweight (< 2.26, 2.3–3.175, 3.2–4.54, > 4.54 kg).

Table 4

Risk of Crohn's Disease and Ulcerative Colitis According to Preterm Birth Status*

	No	Yes
Person-Years	3,155,833	217,893
Crohn's Disease		
Cases	235	13
Age-Adjusted Incidence§	7	6
Age-Adjusted, 95% CI	1.00	0.79 (0.45–1.38)
MV-Adjusted, 95% CI†	1.00	0.69 (0.37–1.29)
Ulcerative Colitis		
Cases	288	16
Age-Adjusted Incidence§	9	7
Age-Adjusted, 95% CI	1.00	0.78 (0.47–1.29)
MV-Adjusted, 95% CI†	1.00	0.81 (0.46–1.43)

Abbreviations: confidence interval (CI), multivariate (MV)

*Preterm birth is defined as being born 2 or more weeks premature.

§Reported as number of cases per 100,000 person-years.

†Adjusted for age (months), cohort (NHSI vs. NHSII), BMI (<20, 20–24,9, 25–29.9, ≥ 30 kg/m^2), smoking (never, past, current), history of diabetes in the mother (yes, no), maternal smoking during pregnancy (yes, no, unknown), ever use of oral contraceptives (yes, no), having been breastfed (yes, no), and birthweight (< 2.26, 2.3–3.175, 3.2–4.54, > 4.54 kg).

Table 5

Risk of Crohn's Disease and Ulcerative Colitis According to Birthweight

	Birthweight (kg)			
	< 2.26	**2.3–3.175**	**3.2–4.54**	**> 4.54**
Person-Years	321,695	1,033,922	1,565,129	452,981
Crohn's Disease				
Cases	25	73	113	37
Age-Adjusted Incidence[§]	8	7	7	8
Age-Adjusted, 95% CI	1.13 (0.72–1.79)	1.00	1.03 (0.76–1.38)	1.13 (0.76–1.69)
MV-Adjusted, 95% CI[†]	1.29 (0.79–2.11)	1.00	1.00 (0.74–1.34)	1.06 (0.71–1.58)
Ulcerative Colitis				
Cases	23	95	143	43
Age-Adjusted Incidence[§]	7	9	9	9
Age-Adjusted, 95% CI	0.83 (0.52–1.31)	1.00	0.98 (0.76–1.27)	1.02 (0.71–1.47)
MV-Adjusted, 95% CI[†]	0.91 (0.55–1.49)	1.00	0.98 (0.75–1.27)	1.02 (0.71–1.47)

Abbreviations: confidence interval (CI), multivariate (MV)

[§]Reported as number of cases per 100,000 person-years.

[†]Adjusted for age (months), cohort (NHSI vs. NHSII), BMI (<20, 20–24,9, 25–29.9, ≥ 30 kg/m^2), smoking (never, past, current), history of diabetes in the mother (yes, no), maternal smoking during pregnancy (yes, no, unknown), ever use of oral contraceptives (yes, no), prematurity (yes, no), and having been breastfed (yes, no).