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Perinatal Factors and Adult-Onset Lupus

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Abstract

Objective—Some evidence suggests that perinatal factors, including birth weight and breastfeeding, may influence occurrence of autoimmune rheumatic diseases. However, few have investigated these factors in systemic lupus erythematosus (SLE). Therefore we evaluated the role of birth weight, being breastfed, and preterm birth on incident SLE in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

Methods—We studied 87,411 NHS and 98,413 NHSII participants free of SLE at baseline who provided information on perinatal exposures. Among these women, during 26 (NHS) and 14 (NHSII) years of follow-up, 222 incident SLE cases were confirmed (136 NHS and 86 NHSII) by medical record review using American College of Rheumatology criteria. We used stratified Cox models to estimate the association of perinatal factors with SLE adjusting for race, early passive cigarette smoke exposure, and parents' occupation. Random effects meta-analysis was used to compute combined estimates across the two cohorts.

Results—After adjustment for multiple potential confounders, high birth weight (≥10 lbs) was associated with increased rates of SLE compared to normal birth weight (7–8.5lbs) (RR=2.7, 95% CI: 1.2, 5.9) as was being born 2+ weeks preterm (RR=1.9, 95% CI: 1.2, 3.0); however being breastfed was not (RR= 0.8, 95%CI: 0.6, 1.1).

Conclusion—Birth weight ≥10 lbs and preterm birth were both positively associated with incident SLE among women.

Keywords

perinatal; lupus; SLE; epidemiology; Nurses' Health Studies; breastfeeding; preterm birth; birth weight

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Barker's hypothesis, also known as the *fetal origins of adult disease hypothesis*, posits that the fetal environment influences the course of diseases in adulthood(1,2) including coronary heart

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disease (2–4), breast cancer (5,6), and type II diabetes (7). The fetus or infant is exposed to numerous antigens, hormones, immunoglobulins, and cytokines via transplacental pathways in the fetus, or via breastfeeding in the infant. In SLE, these exposures during the plastic developmental period may affect antigenic specificity, thymic development, and lymphocyte selection – all of which might be linked to autoantibody production, loss of tolerance, and immune dysregulation seen in SLE. The epidemiologic evidence for associations of perinatal factors and autoimmune disease is mixed. Some studies have demonstrated an increased risk of autoimmune rheumatic diseases such as Sjogren's syndrome (8) and rheumatoid arthritis (RA) with high birth weight (9),(10), and reduced risk of RA with breastfeeding.(9) In a recent case-control study, birth weight was not associated with SLE.(11)

In this study, we examine the role of birth weight, preterm status, and breastfeeding in the development of SLE among nearly 200,000 women participating in two prospective cohort studies, the Nurses' Health Study and the Nurses' Health Study II.

Methods

Study Population

The Nurses Health Study (NHS) is a prospective cohort of 121,701 U.S. female nurses aged 30 to 55 years at enrollment in 1976. The Nurses Health Study II (NHSII) is a prospective cohort of 116,608 female U.S. nurses who were between the ages of 25 and 42 in 1989 at baseline. Updated information on exposures including weight, diet, smoking, physical activity, health status, and family medical history is collected biennially by mailed questionnaire with response rates consistently over 90% in both cohorts.

Exclusions

We excluded women who reported prevalent SLE at baseline, those who did not answer the questionnaires that assessed perinatal exposures (NHSII 1991 questionnaire, NHS 1992 questionnaire), and those who were not singleton births as their fetal environment may be different. After these exclusions 87,411 NHS and 98,413 NHSII subjects formed the basis of this analysis.

Perinatal Factors

Birth weight—In 1992, NHS participants were asked their birth weight in categories (not sure/< 5 lbs/5 –5.5 lbs/5.6 – 7 lbs/7.1 – 8.5 lbs/8.6– 10 lbs/> 10 lbs). Slightly different categories were used in the 1991 NHSII questionnaire (not sure/<5.5 lbs/5.5 – 6.9 lbs/7 – 8.4 lbs/8.5 – 9.9 lbs/≥10 lbs). For comparability, birth weight was classified in this analysis as: not sure/ <5.5 lbs/5.5–6.9 lbs/7–8.4 lbs/8.5 – 9.9 lbs/≥10 lbs, for both cohorts. Low birth weight was defined to be less than 5.5 pounds and high birth weight was 10 pounds or greater.

Breastfeeding during infancy—On the 1991 NHSII and 1992 NHS questionnaires participants were asked, "Regarding your infancy, were you breastfed?" to which they could answer "yes", "no", or "don't know". Duration of breastfeeding was classified as: not sure, 3 months or less, 4–8 months, and 9+ months.

Preterm births—On the 1991 NHSII and 1992 NHS questionnaires participants were asked, "Regarding your infancy, were you 2+ weeks premature?"

Incident Systemic Lupus Erythematosus

A two-stage case validation process was used to classify SLE. Starting in 1978 (NHS) and 1989 (NHSII) participants were first asked to list physician-diagnosed illnesses and to specify

the date of each diagnosis. Beginning in 1982 (NHS) and 1993 (NHSII), participants were asked specifically about physician diagnosed systemic rheumatic diseases including SLE, RA, scleroderma, Sjogren's syndrome, and mixed connective tissue disease. Those reporting a diagnosis of any one of these were asked to complete a previously validated, connective tissue disease screening questionnaire and for permission to review their medical records.(12,13) Their diagnosis was then confirmed or refuted by medical record review independently by two rheumatologists blinded to the participants' perinatal exposures. Nearly 70% of the medical records reviewed for SLE were confirmed. We defined our primary outcome of incident SLE as three or more ACR criteria in addition to positive impressions by the two reviewers; 136 incident SLE cases in NHS and 86 in NHSII were confirmed. As a secondary outcome we considered at least four ACR criteria from medical record reviews to classify incident, confirmed SLE which yielded 124 and 81 NHS and NHSII participants, respectively.

Additional Covariates

Data were available on additional covariates including early life exposure to passive cigarette smoke, parents' occupations, race/ethnicity, state of residence at birth, maternal diabetes, maternal birth year, and maternal body shape at age 50 from NHS and NHSII questionnaires. In a validation study, self-reported fetal exposure to smoke was compared to the nurse's mother's report of smoking during pregnancy (sensitivity = 85%, specificity=95%). Furthermore, self-reported childhood passive exposure to smoke was a good proxy for fetal exposure as reported by the mother (sensitivity = 88.5%, specificity=87.9%)(14).

Statistical Analyses

Participants' baseline characteristics were analyzed stratified by birth weight and breastfeeding during infancy. Cox proportional hazards models stratified on age and study enrollment time estimated incidence rate ratios (RR) of SLE as a function of perinatal exposures. The proportional hazards assumption was assessed by Wald tests of the time by exposure statistical interactions in Cox models. Among subjects free of disease at baseline (1976 in NHS or 1989 in NHSII) person-time accrued until the diagnosis of SLE, date of death, or return of their last questionnaire. Potential confounders including parents' occupations (as a proxy for socioeconomic status), race/ethnicity, and early life passive cigarette smoke exposure were chosen *a priori* to be included in multivariable stratified Cox models. In identifying potential confounders we considered covariates or proxies of covariates that satisfied the criterion of confounding: risk factor for SLE independent of perinatal factors, associated with perinatal factors in the absence of SLE, and not a downstream consequence of perinatal factors of interest. State of residence at birth, maternal history of diabetes, maternal body shape, and maternal age were also considered as potential confounders after the above covariates were forced into the model. We examined whether the effect of perinatal characteristics on incident SLE varied by maternal diabetes. Meta-analytic techniques were used to summarize results from the two cohorts using the test of heterogeneity and random effects meta-analysis to provide a weighted average of the cohort-specific results (15). When the test of heterogeneity was statistically significant at the 0.05 level, we rejected the null hypothesis of homogeneity and computed the summary estimates using a random effects model; otherwise fixed effects were used to summarize the results of the two cohorts.

Sensitivity Analyses

We conducted sensitivity analyses in which we limited incident SLE to those with at least four ACR criteria in addition to positive reviewers' impressions from the medical record review. To evaluate potential recall bias we conducted a sensitivity analysis, in which we considered only follow-up after exposure ascertainment (1991 in NHSII, 1992 in NHS). A third sensitivity

analysis included participants with self-reported prevalent SLE at baseline. Lastly, we ended follow-up at the time of self-report of connective tissue diseases during in a sensitivity analysis.

Results

As expected, in both cohorts, participants who reported low birth weight were more likely to have parents who smoked. Furthermore, birth weight was positively associated with weight and BMI at age 18 in NHS and NHSII respectively, and participants reporting high birth weight were more likely to have mothers with a history of diabetes (Table 1). Participants who were breastfed during infancy were slightly older, less likely to have parents who smoked during their childhood (Table 2).

Birth weight

High birth weight (≥ 10 lbs) was positively and statistically significantly associated with incident SLE in meta-analysis of the two cohorts (RR=2.7, 95% CI 1.2, 5.9) (Table 3). The suggestion of an association between low birth weight (< 5.5 lbs) and incident SLE in NHSII was not consistent in direction with NHS, nor was it statistically significant with multivariable adjustment for potential confounders. (Table 3)

In post-hoc analysis when we used < 5 lbs as the low birth weight definition in NHS only and adjusted for parents' occupations, childhood smoke exposure, race/ethnicity, and preterm birth we found a non-statistically significant elevated rate of incident SLE (RR=1.8, 95% CI: 0.7, 4.5) with birth weight < 5 lbs.

Preterm Births

Preterm birth by two or more weeks was associated with a two-fold higher rate of SLE in both cohorts and in meta-analytically combined multivariable-adjusted models (RR=1.9, 95% CI: 1.2, 3.0). When preterm status and categorical birth weight were modeled simultaneously in multivariable models, the estimated effect of preterm status on incident SLE persisted (RR=1.9, 95% CI: 1.1, 3.4).

Breastfeeding

In both cohorts, being breastfed during infancy was not associated with incident SLE (Table 3). Among those who reported being breastfed, a large percentage did not know for what duration: NHS (58.2%) and NHSII (30.9%). Among those with known duration of breastfeeding, there was no statistically significant association between duration and SLE incidence.

All analyses were repeated with further adjustment for state of residence at birth, maternal history of diabetes, and maternal age and the results were essentially unchanged.

Sensitivity Analyses

Using the stricter ACR classification of SLE (≥ 4 ACR criteria) in combination with positive impressions from two independent rheumatologists reviewing the participants' medical records, we found similar results in the two cohorts separately and in meta-analytically combined analysis for birth weight (RR_{meta}=2.9, 95% CI: 1.3, 6.4), preterm status (RR_{meta}=2.0, 95% CI: 1.3, 3.2), and breastfeeding exposures (RR_{meta}=0.9, 95% CI: 0.6, 1.2). When only person-time and cases accruing after exposure ascertainment were included, the association between high birth weight (≥10 lbs) and incident SLE in NHS alone remained consistent with findings when all cases and person-time were included, though with wider confidence intervals (RR=2.2, 95% CI: 0.3, 17.5). In the NHSII cohort there were no SLE cases

with birth weight ≥ 10 lbs in this restricted analysis. Additionally, when follow-up was terminated at report of connective tissue disease findings were similar.

Discussion

In this study, high birth weight (≥10 lbs) was associated with a higher incidence of adult-onset SLE in women. Low birth weight, defined as less than 5.5 lbs, was not significantly associated with incident SLE. Participants who were born at least two weeks premature had a statistically significant two-fold higher incidence of SLE. Sensitivity analyses did not appreciably change these findings.

Similar to previous findings for RA and Sjogren's syndrome (8–10), we found that high birth weight was associated with an increased incidence of SLE. Given our findings, we estimate that approximately 2% of the SLE cases were associated with high birth weight, although this does not imply a causal link. Coleman and colleagues' case-control study of 23 SLE cases found no significant difference in mean birth weight between cases and controls.(11) However Coleman et al did not specifically consider the extremes of birth weight, in which we were most interested in the present study. Furthermore they included probable SLE cases (defined as ≥ 2 ACR criteria) which may have led to some misclassification of their outcome. In contrast, with our larger number of cases, using a stricter definition of SLE, and modeling birth weight categorically, high birth weight was significantly associated with incident SLE. As seen in Table 1, it is possible that high birth weight is a consequence of maternal diabetes, however when the models were adjusted for maternal diabetes, the effect of birth weight was unchanged, and maternal diabetes was not associated with SLE.

Preterm birth was associated with a two-fold higher incidence of SLE among these adult women. We estimate that 4.7% of the SLE in the population may be associated with preterm birth, however, this does not imply that preterm birth causes SLE. As preterm status is closely related to low birth weight, these two effects may be intertwined. The attenuation of the effect of low birth weight after adjustment for preterm status is consistent with *the birth weight paradox* as described by Hernandez-Diaz and colleagues (16–18); specifically that observed associations between low birth weight and disease may not be causal since low birth weight could be a proxy for other risk factors such as gestational age and intrauterine growth restriction. The remaining association of preterm birth with incidence of SLE after this adjustment suggests that prematurity may increase the risk of SLE in ways other than through birth weight. It is important to note that there were no cases born preterm and weighing > 10 lbs at birth.

A small case-control study suggested a 90% reduction in odds of adult RA when comparing infants who were breastfed during the mother's postnatal stay to those who were not (OR=0.1, 95% CI: 0.0 to 0.4).(9) Studies of autoimmune rheumatic manifestations in children have shown that cases of juvenile RA were less likely to have been breast fed than controls (19) and have also demonstrated a strong inverse association between breast feeding duration greater than three months and rheumatoid factor positivity among a subset of children who were negative for HLA-DR4, a strong genetic risk factor for rheumatoid arthritis (20). In the present study, being breastfed was not statistically significantly associated with SLE incidence.

A link between SLE and birth weight is biologically plausible. An inverse association between birth weight and cortisol responsiveness has been found in several studies and this disrupted cortisol responsiveness may be related to autoimmunity and chronic inflammation.(21,22) Hormonal factors may also link high birth weight and SLE through multiple potential pathways including the positive association between maternal estrogen levels and birth weight suggesting elevated estrogen exposure during fetal development(23). We considered maternal body shape

as a potential confounder because of the positive association between adipose tissue and estrogen, and the ongoing discussion about the role of estrogen and sex hormones in SLE pathogenesis.

The mechanisms behind the association between preterm birth and SLE are not well understood. Whether the consequences or determinants of preterm birth increase the risk of SLE is unknown. It is possible that the underlying pathology of preterm delivery (i.e. infection or pre-eclampsia) which results in changes in the infant's immune system might lead to increased risk of autoimmune disease such as SLE. For instance maternal infection is a strong determinant of preterm birth (24) and infections have been posited in the pathogenesis of SLE (25). The immature immune system of a preterm neonate may be ill suited to respond to the maternal infection thereby leading to long-term insults and alterations to the immune system. Additionally, recent immunologic studies suggest altered lymphocyte homeostasis in the thymus in the development of autoimmunity, and it is interesting to speculate that lymphocytes may be more likely to be auto-reactive if they circumvented the thymic selection in the underdeveloped preterm infant (26).

Limitations and strengths

Our study is not without its limitations. Perinatal exposures were reported years after baseline questionnaires and the primary analysis included cases diagnosed prior to assessment of their exposures. In the sensitivity analyses which only included follow-up after exposure ascertainment, the magnitude and direction of our findings were similar to the findings from the full follow-up period, suggesting that recall bias is unlikely to explain our results. In a validation study among a random sample of NHSII participants and both their mothers' recall and official state documents, self-reported birth weight and breastfeeding during infancy were validated by Troy and colleagues(27). This sample of NHSII participants was oversampled by ethnicity yielding a roughly even distribution across four ethnic groups: African-American, Asian, Caucasian, and Hispanic. The sample included 534 NHSII participants whose mothers had returned completed questionnaires in 1992 as part of this validation.. Additionally Troy et al requested birth records from a sample of states in which at least 40 NHSII participants in this sample were born (n=220). Spearman correlations were calculated to measure correlation between NHSII participant and mother's recall for categorical birth weight (r=0.75) and categorical duration of breastfeeding (r=0.74). In the subsample with state birth records, correlations between NHSII participant and birth records yielded similar results for birth weight (r=0.74)(27). Being breastfed during infancy (yes/no) was also validated in this mother-daughter sample and showed good agreement (82% sensitivity, 86% specificity).(27) Further it is important to note that Troy et al's validation study considered only NHSII participants, and therefore we cannot say with certainty whether the validity of self-reported perinatal characteristics is equivalent in the older NHS cohort. Self-reported preterm birth status has been validated in other studies. A validation study among women 45 years of age and younger (breast cancer cases and population-based controls) from western Washington found that participants recalled their preterm status with 0.63 sensitivity and 0.98 specificity, while another validation study found a correlation of 0.74 comparing medical records to self-report among 17 year olds(28,29).

Though these validation studies suggest that self-report of the perinatal factors of interest was valid and reliable, we cannot exclude the possibility of misclassification. However, given that at the time these data were collected there was little known or explored regarding the role of perinatal factors on SLE incidence, we suspect that this misclassification, if present, is nondifferential with respect to SLE. In the case of dichotomous exposures such as preterm birth and being breastfed, this type of nondifferential misclassification would likely bias towards the null, suggesting that our findings may be an underestimate of the true magnitude.

However, in the case of categorical exposures such as birth weight and breastfeeding duration, we can not predict the direction of this possible bias. Furthermore the high proportion of participants uncertain of the possible duration of their breastfeeding exposure during infancy limits our interpretation of these findings.

By limiting medical record review and validation to participants who screened positively on the connective tissue disease screening questionnaire, we may have misclassified participants with mild or subclinical disease as not having SLE. However the SLE incidence rates in our study were consistent with the published literature and the small number of possible false negatives is insufficient to affect our estimates, due to the large number of true negatives in this sample size of 185,824 women.(30) Additionally any misclassification of SLE that did occur is likely to be non-differential with respect to perinatal characteristics. To address the possible concern that our primary definition of SLE requiring at least three ACR criteria would lead to many false positives, we showed that in sensitivity analyses with SLE defined as at least four ACR criteria results were similar. When unconfirmed, prevalent SLE reports were included as cases, nearly all of the effect estimates were attenuated suggesting substantial misclassification in the self-reported non-validated cases, supporting the importance of medical record review in epidemiologic studies of SLE.

The generalizability of our study is limited to primarily Caucasian females, and to adult onset SLE. We considered a population of women who survived, were healthy enough, and had the resources to pursue an active career in nursing. As such, it is possible that those most susceptible to develop SLE at an early age were not included in these analyses. Also the statistical power of this study is limited as the number of participants stratified by perinatal exposures and case status was small: therefore future work is needed to verify these findings as well as to explore possible effect modification by factors such as maternal diabetes. Although we had some limited data on both the perinatal factors and maternal diabetes, once we stratified our multivariable Cox models by maternal diabetes we found that the data were too sparse to provide any information as to whether effect modification may be present. However the association between high birth weight and SLE was similar when we looked only among those without history of maternal diabetes. In addition these exposures should be investigated among non-Caucasian cohorts, as the risk of SLE in non-Caucasians is substantially higher.

Adjustment for a variety of covariates did not appreciably change our results, although bias due to unmeasured or residual confounding is possible as with all studies based on observational data. For instance, we did not have data on family history of autoimmune diseases, particularly of SLE and the systemic rheumatic diseases (such as Sjogren's syndrome, polymyositis, rheumatoid arthritis) which may share a genetic risk with SLE. We defined preterm delivery as two or more weeks premature. Given the variability and difficulty in pinpointing a precise delivery date, it is possible that our definition of preterm birth led to misclassification; As the data had already been collected in these two cohorts asking about "2 + weeks premature", there was no information to distinguish between mild prematurity and more severe preterm birth. Despite this potential nondifferential misclassification, which would tend to bias toward the null, preterm birth was consistently positively associated with incident SLE.

This study of perinatal exposures and incident SLE in a relatively homogeneous population of well-educated Caucasian women, suggests that preterm status and high birth weight are associated with SLE incidence and warrant further consideration both in epidemiological and mechanistic studies.

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Table 1

Characteristics of the Study Population by Cohort (NHS/NHSII) and Self-Reported Birth Weight. Presented as mean(sd) or %.

	Birth Weight					
	<5.5 lbs	**5.5–7 lbs**	**7–8.5 lbs**	**8.5–10 lbs**	**>10 lbs**	**Not Sure**
NHS Participants (1976)	7052 (8.1%)	21632 (24.8%)	31525 (36.1%)	7788 (8.9%)	1672 (1.9%)	17742 (20.3%)
Age at baseline (yrs)	42 (7.1)	42 (7.1)	42 (7.1)	43 (7.1)	45 (6.6)	46 (6.6)
Mother Smoked in Home	28.0	24.5	22.9	21.8	17.7	20.2
Father Smoked in Home	64.8	62.6	62.2	62.6	61.4	59.9
BMI at age 18	18.7 (7.3)	18.7 (7.1)	19.3 (7.1)	19.4 (7.4)	19.9 (8.0)	18.6 (7.4)
BMI at baseline	23.4 (4.8)	23.1 (4.4)	23.5 (4.6)	24.0 (4.8)	24.5 (5.3)	23.5 (4.5)
Maternal Diabetes	9.1	8.7	9.5	12.2	18.0	10.5
Father's Occupation						
Laborer/Farmer	10.1	10.3	11.0	12.6	13.6	13.8
Crafts/Service/Home	19.9	19.3	19.5	20.1	22.8	20.9
Clerical/Sales	34.6	34.3	34.1	33.6	33.4	30.5
Professional/Managerial	25.9	27.5	26.9	24.6	19.8	21.8
Mother's Occupation						
Laborer/Farmer	0.4	0.4	0.4	0.4	0.7	0.7
Crafts/Service	10.8	9.8	9.5	10.4	11.3	10.5
Clerical/Sales	12.3	11.6	11.6	11.1	10.5	8.6
Professional/Managerial	9.4	9.2	9.3	8.3	8.1	6.8
Housewife	61.6	64.9	65.2	65.6	64.2	63.5
African-American	1.1	1.3	0.8	0.9	1.2	2.4
Hispanic	0.7	0.6	0.5	0.4	0.4	0.9
NHSII Participants (1989)	6542 (6.7%)	27577 (28.0%)	44321 (45.0%)	11205 (11.4%)	1171 (1.2%)	7597 (7.7%)
Age at Baseline (yrs)	35 (4.6)	34 (4.7)	34 (4.7)	34 (4.7)	34 (4.6)	35 (4.5)
Mom Smoked while Pregnant	44.9	34.9	24.0	18.1	11.3	24.9
Mom Smoked in Home	51.1	42.4	33.0	27.7	20.4	35.2
Dad Smoked in Home	63.8	59.3	55.3	53.7	49.5	54.6
BMI at age 18	21.2 (3.6)	21.1 (3.3)	21.3 (3.3)	21.7 (3.4)	22.4 (4.1)	21.1 (3.2)
BMI at baseline	24.4 (5.5)	23.9 (5.0)	24.1 (5.0)	24.5 (5.2)	25.3 (5.9)	23.9 (4.8)

	Birth Weight					
	<5.5 lbs	**5.5–7 lbs**	**7–8.5 lbs**	**8.5–10 lbs**	**>10 lbs**	**Not Sure**
Maternal Diabetes	7.3	6.1	6.7	9.8	18.7	7.5
African-American	2.0	1.8	1.2	1.0	2.2	3.3
Hispanic	1.6	1.5	1.2	1.4	1.5	2.6

Table 2

Study Population Characteristics by Breastfeeding Status in Infancy. Presented as mean(sd) or %.

	Breastfed During Infancy		
	Yes	**No**	**Not Sure**
NHS	47080 (53.9%)	25611 (29.3%)	14720 (16.8%)
Age at Baseline (yrs)	44 (6.9)	40 (6.9)	44 (6.9)
Mother Smoked in Home	19.3	28.5	24.5
Father Smoked in Home	60.6	64.7	61.8
BMI at age 18	19.1 (7.1)	18.9 (7.3)	18.8 (7.4)
BMI at Baseline	23.6 (4.5)	23.2 (4.5)	23.5 (4.5)
Maternal Diabetes	10.4	8.9	9.4
Father's Occupation			
Laborer/Farmer	13.7	8.3	9.8
Crafts/Service/Home	20.4	18.9	19.9
Clerical/Sales	32.8	35.1	32.8
Professional/Managerial	24.4	28.3	25.0
Mother's Occupation			
Laborer/Farmer	0.6	0.3	0.3
Crafts/Service	10.2	9.6	9.7
Clerical/Sales	9.7	13.3	11.0
Professional/Managerial	8.3	9.6	8.7
Housewife	67.5	62.1	58.5
African-American	1.6	0.7	1.4
Hispanic	0.8	0.4	0.5
NHSII	31303 (31.8%)	59845 (60.8%)	7265 (7.4%)
Age at Baseline (yrs)	35 (4.7)	34 (4.6)	35 (4.7)
Pregnant Mom Smoked	21.4	31.2	25.5
Mom Smoked in Home	29.3	39.8	36.4
Dad Smoked in Home	51.5	59.3	56.9
BMI at age 18	21.2 (3.2)	21.3 (3.4)	21.5 (3.5)
BMI at baseline	24.1 (5.0)	24.1 (5.1)	24.3 (5.2)
Maternal Diabetes	7.0	7.2	7.7
African-American	2.1	1.2	2.6
Hispanic	2.2	1.0	1.7

Table 3

Cox proportional hazards model results estimating the effect of perinatal characteristics on SLE incidence.

	SLE Cases		Univariate Cox Model			Multivariable Cox Model		
Models	**NHS n=136**	**NHSII n=86**	***NHS***	***NHSII***	***Combined*†**	***NHS****	***NHSII*****	***Combined*†**
1. Birthweight								
<5.5 lbs	13	9	1.3 (0.7, 2.4)	2.0 (1.0, 4.2)	1.6 (1.0, 2.5)	0.9 (0.4, 1.9)	1.5 (0.6, 3.6)	1.1 (0.6, 2.0)
5.5 – 7 lbs	32	23	1.0 (0.6, 1.6)	1.1 (0.7, 1.9)	1.0 (0.7, 1.5)	1.0 (0.6, 1.6)	1.1 (0.6, 1.8)	1.0 (0.7, 1.5)
7–8.5 lbs	44	33	1.0	1.0	1.0	1.0	1.0	1.0
8.5–10 lbs	12	13	1.1 (0.6, 2.2)	1.5 (0.8, 2.9)	1.3 (0.8, 2.0)	1.2 (0.6, 2.2)	1.5 (0.8, 2.9)	1.3 (0.9, 2.1)
10+ lbs	6	1	3.0 (1.3, 7.0)	1.3 (0.2, 9.2)	2.6 (1.2, 5.7)	3.1 (1.3, 7.3)	1.3 (0.2, 9.5)	2.7 (1.2, 5.9)
2. Preterm[*,**]	11	11	1.9 (1.0, 3.5)	1.9 (1.0, 3.6)	1.9 (1.2, 3.0)	1.9 (1.0, 3.6)	1.9 (1.0, 3.6)	1.9 (1.2, 3.0)
3. Breastfed								
No	43	53	1.0	1.0	1.0	1.0	1.0	1.0
Yes	61	25	0.9 (0.6, 1.3)	0.9 (0.6, 1.5)	0.9 (0.7, 1.2)	0.8 (0.6, 1.3)	0.9 (0.6, 1.5)	0.8 (0.8, 1.1)
4. Breastfed Duration								
≤3 mos	4	3	0.6 (0.2, 1.6)	0.3 (0.1, 1.1)	0.4 (0.2, 1.0)	0.6 (0.2, 1.6)	0.3 (0.1, 1.1)	0.4 (0.2, 1.0)
4–8 mos	5	6	0.5 (0.2, 1.2)	0.8 (0.4, 1.9)	0.7 (0.4, 1.2)	0.5 (0.2, 1.2)	0.8 (0.4, 2.0)	0.6 (0.4, 1.2)
≥9 mos	13	2	1.1 (0.6, 2.0)	0.6 (0.2, 2.6)	1.1 (0.6, 1.8)	1.0 (0.5, 1.9)	0.7 (0.2, 2.7)	0.9 (0.5, 1.7)

[*] multivariable covariates for all NHS analyses included race/ethnicity, age, study time, childhood exposure to passive cigarette smoke and parents' occupations

[**] multivariable covariates for all NHSII analyses included race/ethnicity, age, study time, childhood exposure to smoke and fetal exposure to smoke

[†] all tests of heterogeneity indicated that fixed effects meta-analytic estimates were appropriate (p>0.05).

Model 1 also adjusted for preterm

Models 3 and 4 included preterm and birth weight