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Prenatal and Perinatal Factors and Risk of Multiple Sclerosis

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Abstract

Background—A potential role of prenatal and perinatal exposures in autoimmunity has been hypothesized, but few studies have examined the relation between various prenatal and perinatal factors and risk of multiple sclerosis (MS).

Methods—The study population included participants in the Nurses' Health Studies, 2 prospective cohorts that together comprise 238,381 female nurses, who self-reported exposure to prenatal and perinatal factors. In addition, 35,815 nurses' mothers participated by providing detailed information regarding experiences surrounding their daughter's birth. The following prenatal and perinatal factors were studied in relation to MS: fetal growth, birth season, preterm birth, mode of delivery, maternal weight gain, medical conditions, medication use, diethylstilbestrol exposure, prenatal health care, maternal activity level, maternal obstetric history, parental age, and prenatal and childhood passive smoke exposure.

Results—The sample included 723 confirmed MS cases, including 383 with diagnosis after reporting prenatal and perinatal factors. Few associations were observed. These included an increased risk among women whose mothers reported late initiation of prenatal care (after the first trimester) (27 cases, rate ratio = 1.6; 95% confidence interval = 1.0–2.4), diabetes during pregnancy (2 cases; 10;2.5–42), and maternal prepregnancy overweight/obesity (20 cases; 1.7; 1.0–2.7). Results also suggested a possible increase in incident MS risk among women with prenatal diethylstilbestrol exposure (9 cases; 1.8; 0.93–3.5).

Conclusions—This study provides modest support for a role of prenatal factors in MS risk. The results should be interpreted cautiously due to the limited statistical power, potential for exposure misclassification, and possibility of chance findings.

The etiology of multiple sclerosis (MS) is unknown, although the pathologic features are consistent with an autoimmune mechanism, and roles for both genetic and environmental factors have been suggested.[1,2] The goal of this study was to examine whether prenatal and perinatal factors influence susceptibility to MS. A role of maternal factors is suggested by

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the higher recurrence risk for maternal half-siblings than paternal half-siblings.[3] Prenatal stress is believed to increase the risk of pregnancy complications[4–6] and modulate the hypothalamic-pituitary-adrenal axis, increasing adenocorticotropic hormone, corticotropic-releasing hormone, and cortisol, which may result in impaired immune function and thymic atrophy.[4,7]

Although a few studies have examined the relation between MS risk and month of birth[8,9] and family structure,[10] there are no previous reports directly assessing the effects of prenatal and perinatal exposures. Modest support for a role of pregnancy complications in autoimmunity and immune system development has been provided by studies on other autoimmune diseases. In 2 small case-control studies, high birthweight was associated with an increased risk of Sjögren syndrome[11] and rheumatoid arthritis,[12] but no significant associations were found for maternal disease during pregnancy, previous miscarriage, and gestational age.[11,12] A role of prenatal and perinatal exposures in the causes of type-1 diabetes and atopic conditions has also been suggested, although results are inconsistent.[13,14]

We examined whether in utero and early-life factors relate to the risk of MS among participants in 2 large ongoing prospective cohorts, the Nurses' Health Study (NHS)[15] and Nurses' Health Study II (NHS-II),[16] together comprising more than 200,000 female nurses in the United States.

Methods

Sample

The Nurses' Health Studies—The NHS began in 1976 with 121,701 female nurses ages 30–55 years identified by US nursing boards. Following the initial questionnaire in 1976, these nurses receive a follow-up questionnaire every 2 years to collect information on demographic, lifestyle, and health-related factors, and newly diagnosed diseases. The NHS-II was established in 1989 with 116,680 female US registered nurses ages 25–42 years, followed with similar biennial questionnaires. A participation rate of about 90% has been achieved for both cohorts over time.

Nurses' Mothers' Cohort[17]—In 2001, permission was requested from NHS and NHS-II participants to send a questionnaire to their mothers regarding the nurses' early life exposures. This subcohort was restricted to living nurses who had not been diagnosed with cancer, with living biologic mothers who were free of dementia and other debilitating diseases prohibiting participation. Of these, 52,540 agreed to participate and 39,904 maternal questionnaires were returned. The questionnaire inquired about the mothers' experiences during the pregnancy and birth of their NHS-member daughter. For this study, the nurses' mothers' cohort was restricted to the NHS-II members (n = 35,815), as they comprised 90% of the mother's cohort.

Outcome Assessment

Cases were defined as physician-confirmed MS, as previously described.[18,19] Briefly, cases were identified by self-report on the biennial questionnaires. Nurses were asked to report major illnesses throughout follow-up and were asked specifically about lifetime diagnosis of MS in 1991 and 1992. Subsequent questionnaires collected information on diagnosis within the past 2 years. Permission to review medical records was requested of everyone who reported an MS diagnosis. Diagnoses were confirmed by asking the treating neurologist to complete a questionnaire on diagnostic certainty, clinical history, clinical signs, and laboratory tests. If a neurologist was not involved in diagnosis or failed to respond, the

woman's internist was contacted for diagnostic confirmation. A case was confirmed if the diagnosis was considered definite or probable by the treating neurologist or internist or by medical record review. In 90% of cases the treating physician was a neurologist.

Exposure Assessment

eTable 1 (http://links.lww.com) lists the prenatal and perinatal factors that have been assessed in the Nurses' Health Studies, including the nurses' mothers' cohort. Some factors were included in the NHS and NHS-II biennial questionnaires and were therefore self-reported by the nurses. However, the majority of factors were available only among the nurses' mothers' cohort, included in the questionnaire completed by the nurses' mothers in 2001. eTable 1 shows the sample available for each exposure.

For in utero diethylstilbestrol (DES) exposure, assessed in the NHS-II in 1993, a confirmation questionnaire was sent to all nurses who self-reported DES exposure to classify the level of certainty (very certain, somewhat certain, not certain, or not exposed). The current analysis uses a conservative approach and compares those who were very certain of DES exposure with those who self-reported as nonexposed.

For the maternal-reported exposures in the nurses' mothers' cohort, an obstetric suboptimality score was calculated by adding one point for each positive response to the factors listed in eTable 2 (http://links.lww.com). Due to the rarity of specific complications, optimality scales have been used to examine the relation between overall prenatal health and disease risk. A popular scale is the Gillberg Optimality Scale.[20] The factors on the Gillberg scale are included in our score, in addition to factors included in the maternal questionnaire that were identified by the investigators as potentially representing a suboptimal prenatal environment (lack of prenatal health care, severe nausea, DES exposure, anemia, hospitalization, cigarette smoking, and infertility).

Three factors were hypothesized a priori to be related to maternal immune function during pregnancy: infections during pregnancy, preeclampsia or eclampsia, and proteinuria.[21–23] Preeclampsia is a pregnancy condition of unknown etiology, characterized by hypertension and proteinuria.[24] It may represent maternal immune rejection of the foreign fetus, resulting in a systemic inflammatory response.[22,23] MS risk was examined in relation to exposure to any one or more of these factors by using a dichotomized variable (0 vs. 1+ "immune-related factors").

Statistical Analysis

In the NHS, only MS cases with diagnosis after cohort recruitment (incident cases) were confirmed by requesting medical records. Therefore, women who reported MS with diagnosis before study enrollment were excluded from the NHS analyses. Each participant contributed person-time from the return date of the baseline questionnaire (1976) to the date of diagnosis, death, or end of follow-up (June 2002), whichever came first. In contrast, in the NHS-II, an attempt was made to confirm the MS diagnoses among women with diagnosis before enrollment in the study (prevalent cases) as well as the incident cases. For the NHS-II, person-time began at age 19 and extended to the date of diagnosis, death, or end of follow-up (June 2003), whichever came first. In addition to pooling the incident and prevalent cases, a sensitivity analysis was conducted that was restricted to person-time accrued after the baseline questionnaire, including only the incident cases. The nurses' mothers' cohort analyses were conducted identically to the full NHS-II analyses.

Cox proportional hazards models were used to estimate rate ratios (RRs) and 95% confidence intervals (CIs) for each factor stratified by age in months and calendar year. Multivariate-adjusted Cox models were used to estimate the RR for each factor

simultaneously adjusting for the following MS risk factors assessed in the biennial questionnaires: age, calendar year, latitude at birth (north, middle, or south),[25] sibship size (0, 1, 2+),[26] paternal occupation (professional/managerial vs. other) as a proxy for early life socioeconomic status,[27] pack-years of cigarette smoking (never, <10, 10–24, 25+ packs/year),[18,28] and and total energy-adjusted vitamin D intake during adulthood (quintiles).[19,29,30]

For factors examined in both the NHS and the NHS-II, a summary effect estimate was calculated using a random-effects model after pooling the results by using inverse-variance weighting.[31] Tests of heterogeneity of the main exposures by cohort were performed using the Q statistic. Statistical analyses were performed using SAS9 (SAS institute, Cary, NC).

Linear tests of trend were conducted for the continuous variables (parental age at birth, maternal prepregnancy BMI, birth length, and obstetric suboptimality score), and ordinal categorical variables (birthweight, maternal weight gain, and activity level during pregnancy). We also examined the possibly nonlinear relation between these variables and the risk of MS nonparametrically with stepwise-restricted cubic splines.[32] Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and cubic spline terms.

Cases were accrued both before and after exposure assessment. The nurses' mothers' cohort analyses were primarily retrospective because the exposures were assessed in 2001, 2 years before the last year of case accrual. The analysis of self-reported prenatal smoke exposure was also primarily retrospective because exposure was assessed in 1999 and 2004. However, for the analyses of nurses' self-reported birthweight and preterm birth, 53% of the cases (n = 383) were accrued after exposure data collection (1991–1992), and for self-reported DES exposure 54% of the NHS-II cases (n = 262) were diagnosed after exposure assessment (1993). Due to the possibility of recall bias, for the latter 3 variables, sensitivity analyses were conducted restricted to person-time and case accrual following exposure assessment.

This research was approved by the Institutional Review Board at Brigham and Women's Hospital in Boston, Massachusetts.

Results

The analysis included 593 incident MS cases (241 in the NHS and 352 in the NHS-II), and 130 prevalent cases diagnosed before baseline in the NHS-II.

For all exposure variables other than DES, the conclusions based on the univariate age-adjusted Cox models were the same as those from the multivariate-adjusted analyses. Therefore, only multivariate-adjusted results are presented for all factors except DES.

The effect estimates for the multivariate-adjusted analyses of the relation between MS and the prenatal and perinatal exposures assessed by self-report in the NHS and NHS-II are shown in Table 1. There was no significant heterogeneity in the cohort-specific effect estimates for any factor. Overall, these self-reported factors were not associated with the risk of MS. For birthweight and preterm birth, there was no observed association in the full cohort analyses or in the prospective sensitivity analyses (not shown).

In the analysis of incident cases there was a marginal 50% increased risk among women whose fathers smoked during the prenatal period, and a 24% increased risk among those passively exposed to parental smoking during childhood. When the sample was restricted to women who never smoked in adulthood, these associations were attenuated (paternal

smoking in prenatal period RR = 1.2, 95% CI = 0.67–2.3, childhood passive smoke exposure 1.2; 0.90–1.5).

Table 2 shows the univariate age-adjusted and multivariate-adjusted RRs and 95% CIs for the association between self-reported prenatal DES exposure and risk of MS in the NHS-II. The univariate analysis restricted to all incident cases and that restricted to cases diagnosed after 1993 both showed an increased risk of MS associated with in utero exposure to DES, with effect estimates exceeding 2. However, this association was attenuated in the analysis that included the prevalent cases, and after multivariate adjustment.

The nurses' mothers' subcohort included 184 MS cases (132 incident and 52 prevalent cases). Table 3 shows the multivariate-adjusted RRs and 95% CIs for the factors assessed in the maternal questionnaire with an RR exceeding 1.50 or less than 0.67. In addition, the multivariate-adjusted RR's and 95% CI's for all factors assessed in the maternal questionnaire are listed in eTable 3 (http://links.lww.com).

As shown in Table 3, maternal adiposity was associated with risk of MS. In fact, the decreased risk associated with low maternal prepregnancy BMI persisted after controlling for the BMI of the nurses themselves at age 18 (0.39; 0.18–0.85), although the increased risk observed in relation to maternal overweight and obesity was attenuated after controlling for the nurses' BMI at age 18 (1.5; 0.90–2.4). After controlling for prepregnancy BMI, there was no substantial relation between weight gain and MS (not shown). Although there were no incident cases whose mothers reported diabetes during pregnancy, 2 prevalent cases were exposed, resulting in an observed 10-fold increase in risk associated with maternal diabetes. This association persisted after controlling for maternal prepregnancy BMI (9.6; 2.3–40).

The obstetric suboptimality score was not associated with risk of MS. In the analysis that included both prevalent and incident cases, there was no association between the immune-related maternal complications and risk of MS. However, pregnancies with 1 or more of the factors hypothesized to be related to maternal immune function were associated with a 86% increased risk in the analysis restricted to the incident cases (95% CI = 1.1–3.3).

There was no significant nonlinearity with any continuous or ordinal variable except for maternal age. Because the observed trend for this variable was of an implausible bimodal form, we do not consider it further.

Discussion

In this large prospective cohort study of women with more than 700 MS cases, no convincing association with risk of MS was observed for the majority of prenatal and perinatal factors, including parental age at birth, obstetric history, previous fetal loss, preterm birth, mode of delivery, and morning sickness. However, this exploratory analysis did suggest potential modest associations for some prenatal or perinatal factors including late initiation of prenatal care, lack of parental cohabitation at birth, elevated maternal prepregnancy BMI, and diabetes. In addition, a potential elevated risk of MS was suggested among women exposed prenatally to DES. Various potential early life risk factors warrant further examination in future studies, although their etiologic role, if present, may be modest.

The primary strengths of this study are the use of a large cohort with thorough case ascertainment, confirmation of self-reported diagnosis, and comprehensive data on other risk factors for MS. Despite these important strengths, there are also limitations. First, some exposure misclassification is inevitable as the mothers were asked to recall pregnancies that occurred more than 30 years ago, and the nurses were asked to report events from their own

prenatal period and infancy. Because exposures were assessed in many women after the onset of MS, differential recall of prenatal factors cannot be excluded.

For the NHS-II individuals whose mothers participated in the maternal subcohort, we compared the nurses' reports with their mothers' reports for birthweight, preterm birth, prenatal DES use, and prenatal smoke exposure. The use of nurses' self-reported exposures in the primary analyses is supported by the high level of agreement with their maternal reports. We observed more than 89% agreement for the birthweight categories, preterm birth, DES exposure, and maternal smoking during pregnancy. Troy[33] conducted a similar validation study with 538 NHS-II participants, and also reported a high degree of validity for birthweight and breast-feeding.

A study that assessed the reproducibility and validity of a similar maternal questionnaire provides evidence to support the use of retrospective maternal report of pregnancy-related events from more than 30 years ago.[34] Reliability was examined by comparing questionnaires administered 2 years apart to 146 NHS mothers. A correlation of over 0.7 was achieved for prepregnancy weight, previous fetal loss, pregnancy complications, smoking, alcohol use, caffeine intake, preterm delivery, birthweight, and breast-feeding.[34] This study also compared maternal recall of pregnancy-related factors with data collected during the pregnancies for 154 participants of the National Collaborative Perinatal Project. Validity of maternal recall was suggested by correlations of greater than 0.85 for birthweight and prepregnancy weight, in addition to specificity of over 0.85 for late initiation of prenatal care, smoking, pregnancy complications, preterm delivery, breech birth, and cesarean section. However, sensitivity was weak (<0.60) for late initiation of prenatal care, pregnancy complications, and forceps or vacuum extraction.[34]

This is the first study to assess directly the relation between prenatal DES exposure and risk of MS. DES is a synthetic nonsteroidal estrogen administered to pregnant women between 1940 and 1972 to treat and prevent pregnancy problems. Small preliminary studies have suggested an increased risk of any autoimmune disease[35] or, more broadly, of diseases involving impaired immune function,[36,37] among individuals with prenatal DES exposure. Experimental studies in laboratory animals as well as human case series have also indicated altered immune cell function associated with DES exposure, such as abnormal natural killer cell activity, T cell-mediated immunity, and thymic development.[37–39] Despite the limited statistical power with this very rare exposure, there was modest support for a positive association. Further examination is warranted, especially because the potential association may be generalized to other prenatal hormone exposures.

Both maternal diabetes during pregnancy and increased prepregnancy BMI were suggested risk factors for MS in the maternal subcohort. Interpretation of the association with maternal diabetes must be made cautiously due to the limited data, the fact that only 2 cases were exposed, lack of screening during that time period resulting in likely exposure misclassification, and unknown time of onset (ie, whether it was gestational or preexisting diabetes).

Maternal prepregnancy weight has been shown to affect fetal growth and development, possibly due to the metabolic abnormalities and inflammatory markers associated with obesity.[40,41] It is possible that the hormonal and metabolic disturbances and oxidative stress due to maternal obesity and diabetes can have lasting consequences for offspring health and development.[42,43] A potential positive association between maternal BMI and risk of MS may be due to insufficient prenatal exposure to vitamin D because as high BMI is associated with decreased levels of vitamin D,[44] and vitamin D exposure is suggested to be a protective

factor for MS.[19,45] It is also of note that maternal vitamin D deficiency has been associated with an increased risk of preeclampsia.[46]

Cigarette smoking is an established risk factor for MS.[18] This is the first study to examine the relation between prenatal and childhood passive smoke exposure and MS risk, and no association was observed among never-smokers. The current results do not exclude a moderate effect of early-life passive smoke exposure. They do provide further indirect support for the causal nature of the relation between adult cigarette smoking and MS.

In summary, the results of this study suggest a potential association between select prenatal and perinatal exposures and risk of MS, including in utero DES exposure, late maternal initiation of prenatal care, lack of parental cohabitation at birth, maternal prepregnancy overweight/obesity, diabetes during pregnancy, and exposure to maternal immune-related medical conditions during pregnancy. However, no association was observed for the majority of prenatal and perinatal factors examined. The possibility of associations due to chance must be underscored because 46 factors were studied. The results should also be interpreted cautiously due to the limited statistical power for rare exposures, the exploratory nature of the maternal subcohort analysis, and potential exposure misclassification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Prenatal/Perinatal Factors and Risk of MS in the NHS and NHS-II Cohorts

Variable	No. Participants	No. Cases[a] (prevalent and incident[b])	Multivariate-adjusted[c]: Incident and Prevalent Cases RR(95% CI)	Multivariate-adjusted [c]: Incident cases only RR(95% CI)
Birthweight (lb)				
<5.5	15,243	61	1.22 (0.93–1.60)	1.29 (0.96–1.72)
5.5–8.4[d]	126,881	444	1.0	1.0
8.5–9.9	19,115	69	1.03 (0.75–1.41)	1.13 (0.86–1.49)
10+	2856	10	1.32 (0.67–2.59)	1.08 (0.51–2.28)
P for trend			0.41	0.43
Season of birth				
Spring	58,030	178	1.13 (0.88–1.46)	1.11 (0.83–1.48)
Summer	61,393	182	1.05 (0.70–1.59)	1.04 (0.65–1.68)
Fall	61,392	179	0.93 (0.67–1.28)	0.83 (0.62–1.12)
Winter[d]	57,419	184	1.0	1.0
Twin/multiple birth				
Yes	2950	9	0.96 (0.46–2.00)	0.74 (0.33–1.66)
No[d]	235,287	724	1.0	1.0
Born 2+ wk premature				
Yes	11,481	48	1.14 (0.85–1.54)	1.20 (0.87–1.66)
No[d]	172,699	597	1.0	1.0
Parents smoked at home				
Yes	122,484	459	1.16 (0.93–1.44)	1.24 (1.02–1.51)
No[d]	62,619	163	1.0	1.0
Maternal smoking during pregnancy				
Yes	30,813	128	0.92 (0.75–1.12)	0.97 (0.77–1.21)
No[d]	117,540	400	1.0	1.0
Father smoked during pregnancy[e]				
Yes	37,773	94		1.50 (0.99–2.28)
No[d]	19,926	29		1.0
Maternal age at birth (y)[e]				
14–19	7038	11		0.96 (0.51–1.82)
20–24	32,884	69		1.12 (0.80–1.56)
25–29[d]	36,860	72		1.0
30–34	24,667	57		1.22 (0.86–1.73)
35+	17,186	28		0.88 (0.57–1.37)
P for linear trend				0.27
P for nonlinear trend				0.02
Paternal age at birth(y)[e]				
14–19	1430	5		2.17 (0.87–5.42)

Variable	No. Participants	No. Cases[a] (prevalent and incident[b])	Multivariate-adjusted[c]: Incident and Prevalent Cases RR(95% CI)	Multivariate-adjusted [c]: Incident cases only RR(95% CI)
20–24	16,679	29		0.97 (0.63–1.52)
25–29 [d]	33,971	61		1.0
30–34	29,520	69		1.28 (0.91–1.81)
35–39	17,904	44		1.36 (0.92–2.00)
40+	14,003	22		0.94 (0.57–1.54)
P for trend				0.92

[a] For each factor, the number of cases and participants may not add up to the total number in the study due to missing exposure values.

[b] Incident cases are those diagnosed after cohort recruitment (1976 for NHS and 1989 for NHS-II), prevalent cases are the NHS-II cases diagnosed after age 19 and before cohort recruitment in 1989.

[c] Controlling for age in months, calendar year, latitude at birth, paternal occupation, sibship size, pack-years of smoking in adulthood, quintile of energy-adjusted vitamin D intake.

[d] Reference category.

[e] Variables available only in the NHS and therefore only incident cases were confirmed for these analyses.

Table 2

Prenatal DES Exposure and Risk of MS in the NHS-II

Exposure variable	No. Participants	No. Cases	Univariate Age-adjusted RR (95% CI)	Multivariate-adjusted[a] RR (95% CI)
Incident and Prevalent cases (Follow-up After age 19)[b]				
Prenatal DES exposure				
Yes (very certain)	1461	10	1.56 (0.56–4.30)	1.38 (0.50–3.81)
Not exposed [c]	114111	469	1.0	1.0
Incident Cases Only (Follow-up After 1989)				
Prenatal DES exposure				
Yes (very certain)	1460	9	2.04 (1.05–3.97)	1.81 (0.93–3.53)
Not exposed [c]	113,982	340	1.0	1.0
Follow-up After 1993 Only (Prospective Analysis)				
Prenatal DES exposure				
Yes (very certain)	1459	7	2.16 (1.01–4.58)	1.86 (0.87–3.98)
Not exposed [c]	113,736	255	1.0	1.0

[a] Controlling for age in months, calendar year, latitude at birth, sibship size, pack-years of smoking in adulthood, and quintile of vitamin D intake.

[b] Incident cases are those diagnosed after cohort recruitment (1989–2003), prevalent cases are the cases diagnosed after age 19 and before cohort recruitment in 1989.

[c] Reference category.

Table 3

Prenatal/Perinatal factors and risk of MS in the nurses' mothers' subcohort

Variable	# Participants[a]	# Cases[a] (incident and prevalent[b])	Multivariate-adjusted[c] : Rate Incident cases and prevalent cases Ratio (95% CI)	Multivariate-adjusted[c]: Incident cases only Rate Ratio (95% CI)
Parental factors				
Maternal pre-pregnancy BMI (kg/m^2)				
<18.5	3568	7	0.39 (0.18–0.83)	0.43 (0.19–0.98)
18.5–24.9	27317	149	1.0	1.0
25+	2404	20	1.67 (1.04–2.69)	1.56 (0.89–2.74)
P fortrend			0.001	0.003
Maternal education at birth				
<4 yrs high school	4802	24	0.70 (0.22–2.25)	1.08 (0.66–1.76)
High school graduate[d]	16518	95	1.0	1.0
College	13037	63	1.00 (0.42–2.38)	0.66 (0.44–1.00)
Father born in the US				
Yes[d]	33813	173	1.0	1.0
No	1763	10	1.40 (0.29–6.75)	0.62 (0.22–1.69)
Parents living together at birth				
Yes[d]	34483	179	1.0	1.0
No	422	5	3.95 (1.01–15.37)	3.95 (1.01–15.37)
Maternal medical conditions and healthcare utilization during pregnancy				
Diabetes during pregnancy				
Yes	158	2	10.19 (2.47–42.07)	Not estimable (no cases)
No[d]	33839	173	1.0	
Preeclampsia/toxemia				
Yes	1212	9	1.46 (0.73–2.92)	1.65 (0.79–3.44)
No[d]	33319	167	1.0	1.0 (ref)
Proteinuria				
Yes	580	4	1.99 (0.73–5.43)	1.98 (0.73–5.43)
No[d]	33701	172	1.0	1.0

Variable	# Participants[a]	# Cases[a] (incident and prevalent[b])	Multivariate-adjusted[c] : Rate Incident cases and prevalent cases Ratio (95% CI)	Multivariate-adjusted[c]: Incident cases only Rate Ratio (95% CI)
Infection during pregnancy				
Yes	886	6	1.48 (0.65–3.36)	1.66 (0.67–4.10)
No[d]	33494	171	1.0	1.0
Immune-related factors[e]				
0[d]	32719	162	1.0	1.0
1+	2003	16	1.49 (0.69–3.20)	1.86 (1.05–3.28)
Weight gain during pregnancy (lbs)				
<15	4833	37	1.67 (1.04–2.68)	1.40 (0.88–2.22)
15–29	20650	95	1.0	1.0
30+	7455	42	1.21 (0.84–1.74)	1.16 (0.76–1.77)
P for trend			0.53	0.74
Sleep medication use				
Yes	198	4	3.99 (0.42–37.48)	1.09 (0.15–7.95)
No[d]	34139	175	1.0	1.0
Prenatal care				
None or after 1st trimester	3699	27	1.55 (1.02–2.35)	1.63 (1.00–2.85)
1st trimester[d]	30895	149	1.0	1.0
Maternal activity during pregnancy				
Manual labor at home or work during pregnancy				
Yes	1685	6	0.69 (0.30–1.56)	0.62 (0.22–1.69)
No[d]	33349	170	1.0	1.0
Perinatal factors				
Birth length (inches)				
<18	688	5	1.62 (0.66–3.99)	1.77 (0.65–4.88)
19–22 [d]	24943	123	1.0	1.0
23+	296	1	0.91 (0.13–6.59)	0.91 (0.13–6.59)
P for trend			0.55	0.57
Composite Score				

Variable	# Participants[a]	# Cases[a] (incident and prevalent[b])	Multivariate-adjusted[c] : Rate Incident cases and prevalent cases Ratio (95% CI)	Multivariate-adjusted[c]: Incident cases only Rate Ratio (95% CI)
Obstetric suboptimality score				
0–1[d]	16112	81	1.0	1.0
2	9385	46	0.92 (0.64–1.32)	0.97 (0.63–1.49)
3+	10367	57	1.06 (0.75–1.50)	1.14 (0.76–1.71)
P for trend			0.44	0.49

[a] For each factor, the number of cases and participants may not add up to the total number in the study due to missing exposure values.

[b] Incident cases are those diagnosed after cohort recruitment (1989–2003), prevalent cases are the cases diagnosed after age 19 and before cohort recruitment in 1989

[c] Controlling for age in months, calendar year, latitude at birth, SES (paternal occupation), sibship size, pack-years of smoking in adulthood, quintile of vitamin D intake.

[d] Reference category.

[e] Includes infections, preeclasmpsia/eclampsia, and proteinuria.