

eTable 1 Prenatal and Perinatal Factors Examined

Study samples	Variables
NHS and NHS-II full cohorts ^a	Birthweight (<5.5, 5.5-6.9, 7-8.4, 8.5-9.9, 10+ lbs) ^b , season of birth, multiple birth ^b , preterm vs. term birth ^b , maternal smoking during pregnancy ^b , parental smoking at home during childhood
NHS full cohort only ^a	Maternal age at birth, paternal age at birth, paternal smoking during the year of the nurses' pregnancy
NHS-II full cohort only ^a	In utero DES exposure ^b
Nurses' Mothers Cohort only ^c	Maternal prepregnancy BMI, paternal education level at birth, paternal occupation in infancy/childhood, maternal education at birth, maternal occupation in infancy/childhood, mother born in the US, father born in the US, parents cohabitating at birth, parents owned a home at the time of birth, unsuccessful attempts at pregnancy for >1 year, previous miscarriage(s), previous stillbirth(s), mother working during pregnancy, maternal physical activity level during pregnancy (at home, work, recreationally), manual labor during pregnancy, cesarean delivery, forceps delivery, birth length, maternal medical conditions during pregnancy: anemia, pregnancy-induced hypertension, preeclampsia/toxemia, proteinuria, infections during pregnancy, morning sickness, weight gain during pregnancy, hospitalization during pregnancy, nausea medication use, sleep medication use, timing of initiation of prenatal care

^a Self-reported exposures

^b Also available by maternal report in the nurses' mothers cohort. However, for these variables the exposure was classified by the nurses' self-report.

^c Maternal-reported exposures

eTable 2: Components of the Obstetric Suboptimality Score

Variables (1 point for each positive response)	
Maternal age <20 or >30y	
Low birthweight	
Born 2+ wk early	
Twin pregnancy	
No prenatal health care	
Cesarian delivery	
Forceps use	
Severe nausea	
Sleep medication use	
Nausea medication use	
DES exposure	
Maternal anemia	
Maternal diabetes during pregnancy	
High blood pressure	
Preeclampsia or eclampsia	
Proteinuria	
Maternal infection	
Hospitalization during pregnancy	
Maternal cigarette smoking during pregnancy	
Prior stillbirth	
Prior miscarriage	
Maternal history of infertility	
Total Possible Points = 22	
OSS Distribution in the NHS-II	
<u>Score</u>	<u>Frequency (%)</u>
0	5585 (16%)
1	10506 (29%)
2	9377 (27%)
3	5688 (16%)
4	2718 (8%)
5	1161 (3%)
6	499 (1%)
7	196 (<1%)
8	62 (<1%)
9	24 (<1%)
10	4 (<1%)
11	5 (<1%)
12	1 (<1%)

Table 3: Prenatal and Perinatal Factors and Risk of MS in the Nurses' Mothers' Subcohort

Variable	# Participants ^a	# Cases ^a (incident and prevalent ^b)	Multivariate-adjusted ^c Rate Ratio (95% CI): Incident cases and prevalent cases	Multivariate-adjusted ^c Rate Ratio (95% CI): Incident cases only
Parental factors				
Maternal pre-pregnancy BMI				
<18.5 kg/m ²	3568	7	0.39 (0.18-0.83)	0.43 (0.19-0.98)
18.5-24.9 kg/m ²	27317	149	1.0	1.0
25+ kg/m ²	2404	20	1.67 (1.04-2.69)	1.56 (0.89-2.74)
P for trend			0.001	0.003
Paternal education at birth^d				
<4 yrs high school	6339	32	0.89 (0.59-1.36)	0.85 (0.52-1.39)
High school grad	13142	70	1.0	1.0
College	14756	72	0.99 (0.62-1.57)	0.82 (0.55-1.22)
Paternal occupation in infancy/childhood				
Professional or managerial	10276	58	1.23 (0.89-1.69)	1.23 (0.84-1.79)
Other	23109	113	1.0	1.0
Maternal education at birth				
<4 yrs high school	4802	24	0.70 (0.22-2.25)	1.08 (0.66-1.76)
High school grad	16518	95	1.0	1.0
College	13037	63	1.00 (0.42-2.38)	0.66 (0.44-1.00)
Maternal occupation in infancy/childhood^d				
Professional or managerial	3461	18	1.07 (0.66-1.75)	0.97 (0.53-1.76)
Other	32150	165	1.0	1.0
Father born in the US				
Yes	33813	173	1.0	1.0
No	1763	10	1.40 (0.29-6.75)	0.62 (0.22-1.69)

Variable	# Participants ^a	# Cases ^a (incident and prevalent ^b)	Multivariate-adjusted ^c Rate Ratio (95% CI): Incident cases and prevalent cases	Multivariate-adjusted ^c Rate Ratio (95% CI): Incident cases only
Mother born in the US				
Yes	32820	174	1.0	1.0
No	1833	10	1.28 (0.38-4.34)	0.69 (0.28-1.73)
Parents living together at birth				
Yes	34483	179	1.0	1.0
No	422	5	3.95 (1.01-15.37)	3.95 (1.01-15.37)
Owned a home at time of birth				
Yes	16820	85	1.08 (0.65-1.80)	0.87 (0.61-1.23)
No	15578	98	1.0	1.0
Obstetrical history				
Unsuccessful attempts at pregnancy for >1 year				
Yes	3990	17	0.75 (0.45-1.25)	0.77 (0.43-1.39)
No	29514	166	1.0	1.0
Previous miscarriage				
Yes	12410	68	1.08 (0.79-1.49)	1.20 (0.84-1.71)
No	23051	115	1.0	1.0
2+ previous miscarriages				
Yes	4252	17	0.74 (0.45-1.22)	0.83 (0.47-1.45)
No	31171	166	1.0	1.0
Previous stillbirth				
Yes	1432	10	1.39 (0.73-2.63)	1.36 (0.63-2.93)
No	34432	174	1.0	1.0
Maternal medical conditions and healthcare utilization during pregnancy				
Anemia				
Yes	3652	14	0.77 (0.44-1.33)	0.84 (0.45-1.56)

Variable	# Participants^a	# Cases^a (incident and prevalent^b)	Multivariate-adjusted^c Rate Ratio (95% CI): Incident cases and prevalent cases	Multivariate-adjusted^c Rate Ratio (95% CI): Incident cases only
No	31168	165	1.0	1.0
Diabetes during pregnancy				
Yes	158	2	10.19 (2.47-42.07)	Not estimable (no cases)
No	33839	173	1.0	
Pregnancy-induced hypertension				
Yes	1274	8	1.30 (0.64-2.67)	1.48 (0.68-3.18)
No	33246	169	1.0	1.0
Preeclampsia/toxemia				
Yes	1212	9	1.46 (0.73-2.92)	1.65 (0.79-3.44)
No	33319	167	1.0	1.0
Proteinuria				
Yes	580	4	1.99 (0.73-5.43)	1.98 (0.73-5.43)
No	33701	172	1.0	1.0
Infection during pregnancy				
Yes	886	6	1.48 (0.65-3.36)	1.66 (0.67-4.10)
No	33494	171	1.0	1.0
Immune-related factors^c				
0	32719	162	1.0	1.0
1+	2003	16	1.49 (0.69-3.20)	1.86 (1.05-3.28)
Morning sickness				
Yes	23861	131	1.27 (0.92-1.76)	1.37 (0.93-2.02)
No	11774	51	1.0	1.0
Weight gain during pregnancy				
<15 lbs	4833	37	1.67 (1.04-2.68)	1.40 (0.88-2.22)
15-29 lbs	20650	95	1.0	1.0

Variable	# Participants^a	# Cases^a (incident and prevalent^b)	Multivariate-adjusted^c Rate Ratio (95% CI): Incident cases and prevalent cases	Multivariate-adjusted^c Rate Ratio (95% CI): Incident cases only
30+ lbs	7455	42	1.21 (0.84-1.74)	1.16 (0.76-1.77)
P for trend			0.53	0.74
Hospitalized during pregnancy				
Yes	1463	7	1.04 (0.48-2.22)	0.78 (0.29-2.12)
No	34189	174	1.0	1.0
Medication use in pregnancy				
Yes	4420	24	1.21 (0.57-2.57)	0.84 (0.48-1.48)
No	29543	152	1.0	1.0
Nausea medication use				
Yes	3552	18	1.17 (0.53-2.55)	0.80 (0.42-1.53)
No	31402	162	1.0	1.0
Sleep medication use				
Yes	198	4	3.99 (0.42-37.48)	1.09 (0.15-7.95)
No	34139	175	1.0	1.0
DES use				
Yes	928	6	1.13 (0.50-2.57)	1.24 (0.50-3.06)
No	31715	166	1.0	1.0
Prenatal care				
None or after 1 st tri	3699	27	1.55 (1.02-2.35)	1.63 (1.00-2.85)
1 st trimester	30895	149	1.0	1.0
Maternal activity during pregnancy				
Mother worked during pregnancy				
Yes	11743	53	0.81 (0.58-1.12)	0.76 (0.51-1.12)
No	23868	130	1.0	1.0
Physically active during				

Variable	# Participants ^a	# Cases ^a (incident and prevalent ^b)	Multivariate-adjusted ^c Rate Ratio (95% CI): Incident cases and prevalent cases	Multivariate-adjusted ^c Rate Ratio (95% CI): Incident cases only
pregnancy at home, work, or recreationally^f				
Yes	33014	166	1.0	1.0
No	2632	15	1.12 (0.66-1.91)	1.14 (0.61-2.12)
Activity level during pregnancy^g				
Low activity	10715	61	1.17 (0.83-1.65)	1.17 (0.79-1.72)
Moderately active	12497	71	1.0	1.0
High activity	10670	51	1.11 (0.49-2.51)	0.76 (0.49-1.19)
P for trend			0.98	0.05
Manual labor at home or work during pregnancy				
Yes	1685	6	0.69 (0.30-1.56)	0.62 (0.22-1.69)
No	33349	170	1.0	1.0
Perinatal factors				
Cesarean delivery				
Yes	1179	3	0.67 (0.21-2.12)	0.67 (0.21-2.12)
No	33571	180	1.0	1.0
Forceps delivery				
Yes	7298	43	1.09 (0.76-1.56)	1.15 (0.76-1.74)
No	20463	108	1.0	1.0
Birth length				
<18 inches	688	5	1.62 (0.66-3.99)	1.77 (0.65-4.88)
19-22 inches	24943	123	1.0	1.0
23+ inches	296	1	0.91 (0.13-6.59)	0.91 (0.13-6.59)
P for trend			0.55	0.57

Variable	# Participants ^a	# Cases ^a (incident and prevalent ^b)	Multivariate-adjusted ^c Rate Ratio (95% CI): Incident cases and prevalent cases	Multivariate-adjusted ^c Rate Ratio (95% CI): Incident cases only
Composite Score				
OSS				
0-1	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 Analysis not adjusted for paternal occupation

^e Includes infections, preeclampsia/eclampsia, and proteinuria

^f “No”: not working or mostly sitting and standing at work AND mostly sitting, walking, and standing in the home AND mostly inactive recreationally (less than the equivalent of walking half a mile a day); “Yes”: having a job that requires mostly walking or heavy labor OR mostly active housework or heavy manual work while at home OR recreationally active (equivalent to walking one or miles a day)

^g “low activity”: no walking or regular exercise or the equivalent to walking a half a mile or less a day; “moderately active”: equivalent to walking about 1 mile every day; “high activity”: equivalent to walking 2 or more miles every day