

Maternal and Perinatal Exposures Are Associated With Risk for Pediatric-Onset Multiple Sclerosis

Jennifer S. Graves, MD, PhD, MAS,^a Tanuja Chitnis, MD,^b Bianca Weinstock-Guttman, MD,^c Jennifer Rubin, MD,^d Aaron S. Zelikovitch, BS,^d Bardia Nourbakhsh, MD,^a Timothy Simmons, MS,^e Michael Waltz, MSc,^e T. Charles Casper, PhD,^e Emmanuelle Waubant, MD, PhD,^a on behalf of the Network of Pediatric Multiple Sclerosis Centers

abstract

OBJECTIVE: To determine if prenatal, pregnancy, or postpartum-related environmental factors are associated with multiple sclerosis (MS) risk in children.

METHODS: This is a case-control study of children with MS or clinically isolated syndrome and healthy controls enrolled at 16 clinics participating in the US Network of Pediatric MS Centers. Parents completed a comprehensive environmental questionnaire, including the capture of pregnancy and perinatal factors. Case status was confirmed by a panel of 3 pediatric MS specialists. Multivariable logistic regression analyses were used to determine association of these environmental factors with case status, adjusting for age, sex, race, ethnicity, US birth region, and socioeconomic status.

RESULTS: Questionnaire responses were available for 265 eligible cases (median age 15.7 years, 62% girls) and 412 healthy controls (median age 14.6, 54% girls). In the primary multivariable analysis, maternal illness during pregnancy was associated with 2.3-fold increase in odds to have MS (95% confidence interval [CI] 1.20–4.21, $P = .01$) and cesarean delivery with 60% reduction (95% CI 0.20–0.82, $P = .01$). In a model adjusted for these variables, maternal age and BMI, tobacco smoke exposure, and breastfeeding were not associated with odds to have MS. In the secondary analyses, after adjustment for age, sex, race, ethnicity, and socioeconomic status, having a father who worked in a gardening-related occupation (odds ratio [OR] 2.18, 95% CI 1.14–4.16, $P = .02$) or any use in household of pesticide-related products (OR 1.73, 95% CI 1.06–2.81, $P = .03$) were both associated with increased odds to have pediatric MS.

CONCLUSION Cesarean delivery and maternal health during pregnancy may influence risk for pediatric-onset MS. We report a new possible association of pesticide-related environmental exposures with pediatric MS that warrants further investigation and replication.



^aPediatric Multiple Sclerosis Center, University of California San Francisco, San Francisco, California; ^bPartners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, Boston, Massachusetts; ^cJacobs Neurological Institute, University of Buffalo, Buffalo, New York; ^dLurie Children's Hospital of Chicago, Chicago, Illinois; and ^eData Coordinating and Analysis Center, University of Utah, Salt Lake City, Utah

Dr Graves designed the study, contributed to the statistical analysis plan, and wrote the manuscript; Drs Chitnis, Weinstock-Guttman, Rubin, and Zelikovich contributed to study design and edited the manuscript for content; Dr Nourbakhsh reviewed analyzed data and edited the manuscript for content; Mr Waltz and Mr Simmons performed statistical analysis and edited the manuscript for content; Dr Casper contributed to the statistical analysis plan and performed statistical analysis and edited the manuscript for content; Dr Waubant designed the study, obtained funding, and edited the manuscript for content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

WHAT'S KNOWN ON THIS SUBJECT: Previous studies of autoimmune diseases and pregnancy-related risk factors have implicated breastfeeding as protective. Many of these studies have been done in adults with potential for recall bias and without adjustment for other early risk factors.

WHAT THIS STUDY ADDS: Our study does not confirm a role for breastfeeding in MS risk, but suggests that maternal illness, mode of delivery, and perinatal exposure to pesticides may contribute to risk.

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The relative contributions and timing of environmental exposures that promote multiple sclerosis (MS) onset are not clearly defined. In particular, it is not known how early-life factors near time of gestation may participate. Exposures during pregnancy and breastfeeding have been associated with juvenile diabetes and arthritis,¹⁻⁹ suggesting that early-life environment may be critical to the development of autoimmune disorders. Understanding the role of these factors is important for advancing knowledge of the molecular processes contributing to MS and ultimately the design of prevention strategies.¹⁰

In the few studies available for perinatal risk factors in adult-onset MS, lack of and reduced duration of breastfeeding have been associated with MS risk,^{11,12} and 2 previous publications on the mode of delivery and MS risk had differing results, one showing increased risk with cesarean delivery and the other demonstrating no effect.^{13,14} These studies, however, have not consistently adjusted for other upstream maternal factors, such as maternal illness in pregnancy or maternal age and BMI, which may influence delivery complications and breastfeeding choices. The potential impact of maternal illness during pregnancy and resulting physiologic stress or antigen exposure to the fetus has not been directly addressed in studies of MS risk. Also unaddressed have been potential toxic exposures during gestation. Previous data in adults have suggested that exposure to organic solvents may increase risk for MS.¹⁵⁻¹⁷ It is not known whether certain occupational, behavioral, or household exposures during gestation influence MS risk. Smoking cigarettes is a well-known MS risk factor,^{18,19} but whether maternal or paternal smoking contributes to risk is not as clear.

Studying the effects of pregnancy-related exposures in pediatric-onset MS offers several advantages. Mothers of patients directly contribute to data acquisition rather than relying on memories of adult patients with MS. There is closer proximity of the exposure to symptom onset and fewer effects from diminished quality of recall over time. Finally, it is possible that MS onset in childhood, rather than adulthood, is in part related to higher environmental exposures that may thus be easier to detect.

In one of the largest well-characterized cohorts of new-onset pediatric MS, we sought to determine if prenatal, pregnancy, or postpartum-related environmental factors are associated with MS risk in children.

METHODS

Subjects and Design

This was a case-control study of children with MS or clinically isolated syndrome and healthy controls enrolled at 16 clinics, most of which participate in the US Network of Pediatric MS Centers. Institutional review board approval was obtained at all participating sites and written informed consent was obtained from parents and assent from adolescent subjects. Case status was determined by the treating neurologist and confirmed by a panel of 3 pediatric MS specialists by using published diagnostic criteria for pediatric demyelinating diseases.^{20,21} Cases were enrolled within 4 years of disease onset and had to have at least 2 silent T2-bright foci on magnetic resonance imaging. Healthy pediatric subjects were recruited at primary care, urgent care, and other clinics at the same institutions from which cases were enrolled. Inclusion criteria for healthy subjects were (1) absence of any autoimmune disease, except asthma and eczema; and (2) not having a parent with

MS. Parents of subjects reported demographic data, including race and ethnicity according to National Institutes of Health guidelines, age, and socioeconomic factors, including level of education of both parents.

Environmental Questionnaire

Parents completed a comprehensive environmental questionnaire (<http://www.usnpsc.org/Documents/EnvironmentalAssessment.pdf>), including the capture of pregnancy and perinatal factors. These questionnaires were completed on either a paper form or by electronic entry. Study staff reviewed for completeness and queries were made for missing data. This environmental questionnaire was developed by Drs Waubant and Barcellos based on previous questionnaires used in MS and other autoimmune disorders, such as diabetes.⁶ Questionnaires were tested in 30 families at the University of California, San Francisco, before finalization to identify wording problems that could jeopardize understanding of specific questions and areas with poor completion, which were then removed. Afterward, the coauthors of this work reviewed the questionnaire to shorten it and removed questions of interest for which recall would be extremely unreliable. For this study, only questions pertaining to time periods from 3 months before conception through first of life with adequate response rates (>85%) were included. As appropriate, summary variables were created a priori (before analysis) to reflect sum of similar exposures. For example, different plant pesticides used were combined into 1 variable. A variable for maternal illness in pregnancy was created that included having the flu, pneumonia, sore throat, tonsillitis, bronchitis, chronic earache, severe asthma, sinus infection, diarrhea/gastroenteritis, rash, skin infection, kidney infection, jaundice, high blood pressure (other than preeclampsia),

anemia, fever, incompetent cervix, abruptio placenta, premature rupture of membranes, or prolonged labor. Given frequency of the diseases, preeclampsia and maternal diabetes were analyzed separately.

Statistical Methods

All analyses were performed by using SAS Version 9.4 (SAS Institute, Cary, NC). We described the cases and controls by using frequencies and percentages for the categorical variables and medians, interquartile ranges (25th percentile and 75th percentile), for continuous variables. We compared characteristics between cases and controls by using χ^2 tests or Kruskal-Wallis tests. Due to varying rates of missing data, we reported the counts for patients with data available. Descriptions included the child's age at onset (for cases), child's age at consent, sex, race, ethnicity, primary payer type group, US birth region, and the highest education group the biological mother and father had achieved at the time of the child's birth. Pregnancy-related risk factors were also compared between cases and controls by using χ^2 tests or Kruskal-Wallis tests. Risk factors included mother's prepregnancy BMI, mother's age at time of pregnancy, birth order, breastfeeding within first 2 years of life, delivery method, birth complications, pregnancy-related illness, maternal diabetes, maternal preeclampsia, day care exposure, various smoking-related risks, and vitamin D supplementation.

Multivariable logistic regression analyses were used to determine association of perinatal environmental factors with case status adjusting for age, sex, race, ethnicity, mother's education, and US region. For the primary analysis of hypothesis-driven pregnancy-related risk factors, mutual adjustments for all predictors of interest were made in the final model. We checked summaries of

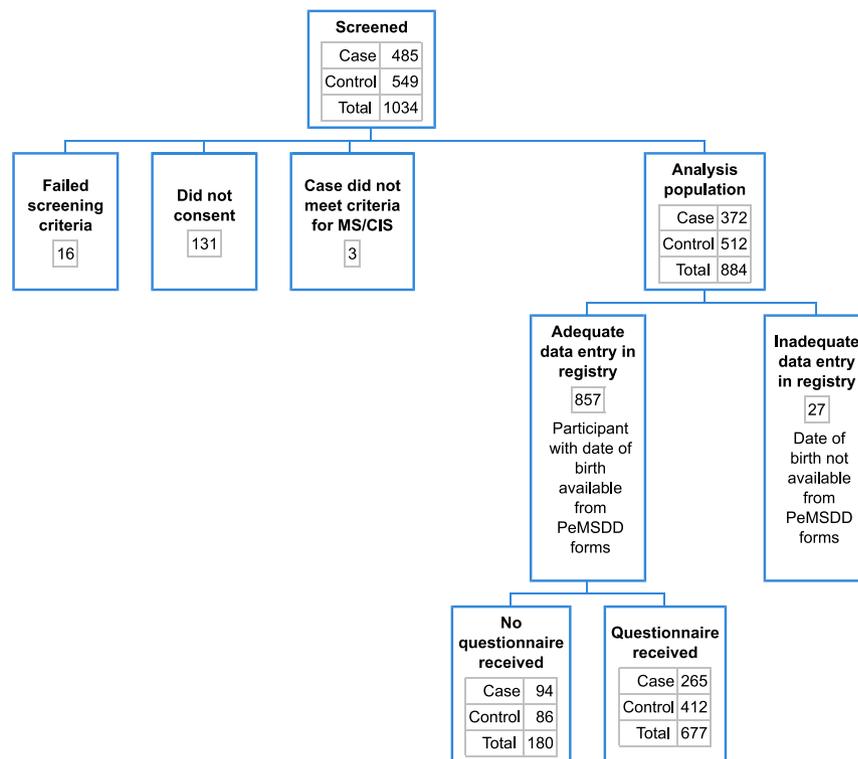


FIGURE 1

Case and control enrollment and inclusion. CIS, clinically isolated syndrome; PeMSDD, Pediatric MS Database.

model fit and diagnostics, including residuals, observation influence, and consistency of the results as variables were added or removed. Variables strongly collinear (eg, birth order) with primary factors of interest (eg, maternal age) were not included in the final multivariable model out of concern for unstable model effects. We also performed exploratory analyses for other environmental exposures during the period of 3 months before conception through the first year of life, again adjusting for age, sex, race, ethnicity, and mother's education.

RESULTS

Questionnaire responses were available for 265 eligible cases (median age 15.7 years, 62% girls) and 412 healthy controls (median age 14.6 years, 54% girls) enrolled between November 2011 and August 2015 (Fig 1). When comparing the demographics of the survey

responders with the nonresponders, we found that more controls (83%) responded than cases (74%). There was no significant difference by sex, but responses varied by race, and Hispanic individuals (76%) were less likely to respond than non-Hispanic individuals (86%). Table 1 describes the subjects' characteristics. There were no significant differences in race between cases and controls ($P = .38$, Table 1), but cases were more likely to be of Hispanic ethnicity than controls (29% vs 17%, $P < .01$). Both the mother's ($P < .01$) and the father's ($P < .01$) highest level of education differed between cases and controls, as well as US birth region ($P = .03$) (Table 1).

Maternal Factors in Pregnancy: Primary Analysis

Differences in frequencies of pregnancy-related maternal factors, including mode of delivery, illnesses during pregnancy, tobacco smoke exposures, vitamin D use, and

breastfeeding, are presented in Table 2. Mother's education was significantly associated with risk of MS, with an odds ratio of 0.33 for college education versus high school or lower (95% confidence interval [CI] 0.15–0.72, $P = .01$) and was included in all models. As previously reported, we observed an association of birth order with case status (Table 2). Birth order, however, was collinear with maternal age and not significantly associated with other maternal factors and thus was not included in the final multivariable model in Table 3. In multivariable analysis, with mutual adjustment of pregnancy risk factors of interest as well as adjustment for sex, race, ethnicity, US region, and socioeconomic status (Table 3), maternal illness other than diabetes and preeclampsia during pregnancy was associated with 2.3-fold increase in odds to have MS (95% CI 1.20–4.21, $P = .01$). Furthermore, cesarean delivery was associated with a 60% reduction (95% CI 0.20–0.82, $P = .01$). In a model adjusted for these variables, maternal age and BMI, tobacco smoke exposure, day care, and breastfeeding were not associated with MS risk (Table 3).

Although appropriate adjustments were made in the multivariable model, to further verify that ethnic and socioeconomic differences in the cases and controls did not drive the main effects observed for maternal illness and mode of delivery, we performed a stratified analysis for mothers with college education and above versus those with high school or less education and for Hispanic and non-Hispanic children. The stratified analyses provided results that were consistent with the results for the full cohort (Supplemental Tables 6–9).

Exploratory Analyses

We performed additional exploratory analyses of environmental exposures during the period of 3 months before

TABLE 1 Subject Characteristics

	Control ($n = 412$)	Case ($n = 265$)	P
Child's age at disease onset, median (IQR)	—	15.0 (12.6–16.4)	
Child's age at consent, median (IQR)	14.6 (11.8–17.1)	15.7 (13.5–17.3)	.01 ^a
The biological mother's age at her birthday in the year the child was born, median (IQR)	29 (24–33)	28 (23–32)	.02 ^a
Sex (% female)	224 (54)	165 (62)	.04 ^b
Subject race category, n (%)			.38 ^b
White	280 (71)	173 (70)	
Black	71 (18)	41 (17)	
Asian	19 (5)	9 (4)	
Other	26 (7)	25 (10)	
Subject ethnicity, n (%)			<.01 ^b
Hispanic or Latino	68 (17)	78 (29)	
Not Hispanic or Latino	332 (81)	178 (67)	
Unknown or not reported	12 (3)	9 (3)	
Primary payer type group, n (%)			.07 ^b
Commercial insurance	257 (62)	143 (54)	
Other, including self-pay and government insurance	139 (34)	106 (40)	
Unknown	16 (4)	16 (6)	
Highest education category the biological mother had achieved at the time of the child's birth, n (%)			<.01 ^b
High school or lower	71 (19)	82 (34)	
College	237 (63)	125 (51)	
Graduate school	44 (12)	22 (9)	
Other	25 (7)	15 (6)	
Highest education category of the biological father, n (%)			<.01 ^b
High school or lower	86 (25)	88 (41)	
College	178 (51)	107 (49)	
Graduate school	62 (18)	15 (7)	
Other	20 (6)	7 (3)	
US birth region, n (%)			.03 ^b
Northeast	102 (27)	94 (39)	
South	96 (25)	53 (22)	
Midwest	40 (11)	24 (10)	
West	139 (37)	73 (30)	

IQR, interquartile range.

^a Kruskal-Wallis test.

^b χ^2 test of no association.

TABLE 2 Unadjusted Pregnancy-related Risk Factors

	Controls	Cases	P
Maternal BMI before pregnancy, median (IQR)	23.0 (20.6–26.6)	23.5 (20.6–27.5)	.21 ^a
Maternal age at birth of child, median (IQR)	29 (24–33)	28 (23–32)	.02 ^a
Birth order, median (IQR)	2 (1–2)	2 (1–3)	.01 ^a
Breastfeeding in first 2 years of life	306 (75)	176 (68)	.05 ^b
Delivery by cesarean	90 (23)	43 (17)	.05 ^b
Any birth complications in the first 2 weeks of life	140 (37)	92 (39)	.64 ^b
Maternal illness without diabetes or preeclampsia	166 (54)	126 (60)	.16 ^b
Maternal diabetes (including gestational diabetes)	10 (3)	10 (4)	.29 ^b
Preeclampsia	11 (3)	6 (2)	.75 ^b
Day care first year of life	236 (60)	133 (53)	.06 ^b
Tobacco smoke exposure	127 (35)	96 (44)	.03 ^b
Vitamin D supplementation during pregnancy	34 (11)	14 (7)	.08 ^b

Values are n (%) unless otherwise noted.

^a Kruskal-Wallis Test.

^b χ^2 test of no association.

conception through the first year of life. For all potential risk factors, we adjusted for age, sex, race, ethnicity, and socioeconomic status. Factors

associated with the odds to have pediatric-onset MS that reached nominal statistical significance of $P < .05$ are listed in Table 4. As

TABLE 3 Multivariable Analysis of Pregnancy-Related Risk Factors With Mutual Adjustment

	OR	95% CI	P
Maternal BMI before pregnancy	1.04	0.98–1.09	.18
Maternal age at birth of child	1.00	0.95–1.06	.93
Breastfeeding in first 2 years of life	0.85	0.45–1.61	.62
Delivery by cesarean	0.40	0.20–0.82	.01
Any birth complications in the first 2 weeks of life	1.37	0.76–2.47	.30
Maternal illness without diabetes or preeclampsia	2.25	1.20–4.21	.01
Maternal diabetes, including gestational diabetes	3.32	0.82–13.48	.09
Preeclampsia	1.23	0.31–4.87	.76
Day care first year of life	0.75	0.41–1.34	.33
Tobacco smoke exposure	0.63	0.34–1.17	.14
Vitamin D supplementation during pregnancy	0.40	0.13–1.23	.11

Also adjusted for age, sex, race, ethnicity, mother's education, and US region.

these were exploratory analyses, the *P* values presented were not corrected for multiple comparisons. The additional predictors that were evaluated, but which had $P \geq .05$, are presented in Supplemental Table 5.

Variables of interest in this exploratory analysis included those related to exposure to gardening and pesticides. Having a father who worked in a gardening-related occupation (odds ratio [OR] 2.18, 95% CI 1.14–4.16, $P = .02$) or any use in subject's household of plant-related pesticide product from 3 months before pregnancy through the first year of life (OR 1.73, 95% CI 1.06–2.81, $P = .03$) were both associated with increased odds to have pediatric MS after adjustment for age, sex, race, ethnicity, and socioeconomic status. Other variables associated with increased odds to have MS included having a dog that slept in the house, higher father's

BMI, number of children in the household, and a prolonged hospital stay for the infant after birth. Month of birth ($P = .95$) and birth weight ($P = .46$) were not associated with odds of MS (Supplemental Table 5). We examined exposures to adhesives or paint thinner petroleum products. Although there was no statistically significant association of these exposures in the household during the peripregnancy period (OR 1.22, 95% CI 0.79–1.89, $P = .36$, Supplemental Table 5), exposure after age 1 was strongly associated with a twofold higher risk of MS (OR 2.02, 95% CI 1.23–3.29, $P < .01$).

DISCUSSION

Our study leverages a unique dataset of early-life exposures. We have identified maternal illness during pregnancy as a potential risk factor for pediatric-onset MS, whereas delivery by cesarean may

be protective. We did not confirm breastfeeding as a protective factor once adjustment was made for the previously mentioned factors. Our exploratory analyses suggest exposure to pesticides in the perinatal period may increase MS risk and exposure to petroleum-based organic solvents may be most relevant after the first year of life.

Mechanisms by which maternal illness in pregnancy may be associated with MS risk include stress-mediated changes, such as elevated glucocorticoid levels, placental insufficiency, metabolic abnormalities, including hyperglycemia, or infectious or immune-mediated exposures.^{5,22–24} Data from animal models, including the murine model of MS, experimental autoimmune encephalitis, have suggested that pathogen exposures during gestation may have prolonged effects on immune responses in the offspring. Certain antigens may increase proinflammatory cytokines, including interleukin-6 and drive a T-helper cell 17 phenotype that may persist in the offspring even into adulthood.^{25,26}

Although we found a protective effect of cesarean delivery on the odds of having pediatric-onset MS, this contrasts to the previously reported deleterious or neutral effect of cesarean delivery on adult-onset MS risk. Being delivered by cesarean

TABLE 4 Exploratory Analysis of Perinatal Exposures

	Cases Exposed ^a	Controls Exposed	OR	95% CI	P
Infant prolonged hospital stay	30	32	1.79	1.00–3.19	.05
Other children in the household before age 6	208	297	1.77	1.13–2.79	.01
Liked all foods versus picky eating first 2 y of life	119	162	1.53	1.08–2.18	.02
Father's BMI before pregnancy (per unit BMI)	—	—	1.05	1.00–1.10	.04
Mother has freckles	64	152	0.50	0.34–0.74	<.01
Father has worked regularly in gardening/farm work	24	22	2.18	1.14–4.16	.02
Household use of plant/tree-related pesticides in perinatal period through first year of life	12	10	1.73	1.06–2.81	.03
Dog slept in house during pregnancy	69	94	1.92	1.03–3.60	.04
Prenatal use of B vitamins	27	77	0.57	0.34–0.95	.03
Use of nausea medication in pregnancy	8	35	0.33	0.15–0.74	<.01

Adjusted for age, sex, race, ethnicity, and mother's highest level of education.

^a Exposure counts are out of total of $n = 265$ cases and $n = 412$ controls.

was associated with increased risk of developing adult-onset MS in a sibling-matched case-control study from Iran,¹³ whereas no association was reported in a nationwide Danish cohort.¹⁴ The discrepancy between these studies might be due to racial or age of MS onset differences, but also control characteristics. Patients of the first study were all Iranian, with a mean age of MS onset of 27.4 years, whereas patients in the second study were all of Danish-born parents and most of them had adult-onset MS. Most patients in our study were white, but a sizeable proportion was Hispanic or nonwhite. It is conceivable that the mode of delivery in various populations has different or opposing effects. The effect of cesarean delivery also may be expected to have more direct impact on pediatric onset given proximity to the exposure. Chance, measurement bias, selection bias, and the effect of unmeasured confounders in these studies might explain some of the differences. In the Iranian study, the mode of delivery was recorded through the adult patient's self-report, which may be more prone to recall bias. The Danish study used the national medical Birth Register, whereas in our study mode of delivery was reported by parents. Last, we adjusted for additional peripregnancy factors that are often upstream of and lead to cesarean delivery (maternal age and BMI, diabetes, preeclampsia) that were not accounted for in these other studies.

Despite the differences in the previously described studies, a potential protective effect of cesarean delivery on early onset of MS is of interest in light of recent findings regarding the microbiome and autoimmune diseases.²⁷⁻²⁹ Cesarean delivery is associated with differences in gut colonization in the first few years of life.^{30,31} These differences may be most relevant in disease development in childhood and become less

relevant in later adult life. In a recent pediatric MS study, we reported substantial differences in type and abundance of taxa in cases versus controls with some taxa such as Christensenellaceae possibly relevant to birth method and impact on disease risk.^{32,33} Future studies will confirm if history of cesarean delivery is associated with microbiota in pediatric MS.

Perinatal exposures may affect MS risk through epigenetic changes that in turn can alter the immune response.³⁴ Embryogenesis is a particularly vulnerable time for DNA modification.^{35,36} Very early in development, for example, DNA methylation patterns are erased and then reestablished during periods of rapid cell division, sexual development, and organogenesis. Maternal illness may affect this process and also environmental toxins. Endocrine disruptors, persistent organic pollutants, arsenic, and several herbicides and insecticides have been associated with epigenetic modifications.³⁷

Although our results of an association of pesticides with MS risk are exploratory and require replication, associations have been reported between pesticides and Parkinson and Alzheimer diseases.³⁸⁻⁴⁰ Pesticides also have been implicated in systemic autoimmune disorders, including systemic lupus erythematosus and are recognized to likely have the strongest impact on the immune system during embryogenesis or early childhood, including on the development of the lymphoid organs.⁴¹⁻⁴³ The time of exposure to pesticides associated with these other disorders is unclear but could occur very early in life.

Inhaled organic solvents largely related to the painting industry have been previously associated with MS risk and this association has additionally been shown to be modified by smoking exposure and *HLA-DRB1*15:01* carrier allele status

(strongest genetic risk factor for MS).¹⁵⁻¹⁷ We did not find a significant association of this risk factor in the perinatal period, but did find twofold higher odds to have MS in those exposed after the first year of life. This fits with the hypothesis that these chemicals increase risk through inhalation and would be less likely to have effect through in utero exposure.

Our results suggest that lower socioeconomic status may be a risk factor for MS. This is consistent with data from a population-representative case-control study from the Northern California Region of the Kaiser Permanente Medical Care Plan⁴⁴ and a recent cohort study demonstrating association of lower perinatal socioeconomic status and risk for rheumatoid arthritis.⁴⁵ These results, however, are in contrast to previous studies that have demonstrated risk associated with higher socioeconomic status.⁴⁶ A systematic review of the association of socioeconomic status with MS risk has found significant heterogeneity in methods and results for 21 studies from 13 countries.⁴⁶ Part of the inconsistent results could in fact be related to the very different ranges of socioeconomic statuses in various regions of the world. We adjusted for socioeconomic status in all of our models, and performed stratified analyses to address concerns of confounding from this variable on the perinatal risk factor associations studied.

In addition to the positive associations discussed previously, some pertinent negative results also were found. In a multivariable model adjusting for other pregnancy-related factors, breastfeeding and maternal BMI were not associated with odds to have MS. Although illness-related stress may affect risk, stressful life events experienced by the mother, such as divorce, trauma, or job loss, were not associated with having MS.

Strengths of our study include that our relatively large dataset is one of few in the field of autoimmune diseases to look at rigorous multivariable models with mutual adjustment for several early-life exposures with potential immune effects. In our primary multivariable model of hypothesis-driven pregnancy-related factors, we were able to address effects of these risk factors simultaneously and avoid potential confounding among these often highly related factors. Additional strengths include enrollment of carefully ascertained cases shortly after MS onset (median less than 1 year), racial and ethnic diversity, and a rigorously phenotyped cohort.

Limitations of our study included the case-control design. Controls were recruited from the same institutions as cases and, thus, likely from the same underlying cohort of children in those catchment areas; however, the cases may derive from a broader geographic area than the healthy controls, as primary care is more widely available than MS specialty care. Although in this pediatric study, there were likely fewer effects from diminished quality of recall over time compared with adult studies, there still may be differential recall between parents with an ill child compared with parents of a healthy child. There were some differences in the participants who completed the questionnaires versus the nonresponders in terms of race and ethnicity. We have observed a discrepancy in socioeconomic status in MS cases versus controls. Despite adjustment in our models for mother's education (adjustment for health insurance type did not

further contribute to the models), residual confounding might have biased our results. It is known that cesarean delivery rates are higher in women with higher socioeconomic status and pesticide exposures also may differ.⁴⁷ However, factors such as work-related exposures and differential health care may instead be mediators of the association of socioeconomic status and MS risk. In the exploratory analyses, results were not statistically significant after adjustment for multiple comparisons, but several variables pertaining to garden work demonstrated association with odds to have MS and in this rare dataset of early-life risk, several factors of interest have been identified that warrant further investigation and replication.

Studying patients with earlier than average age of disease onset provides an outstanding window of opportunity to unravel early-life exposures relevant to disease risk. Our results motivate continuing our recruitment efforts and developing international collaborations as the interactions among early-life exposures associated with autoimmune disease risk may be complex and necessitate large datasets for identification.² For example, for diabetes risk, there may be opposing or synergistic effects of mode of delivery, early enteroviral infections, breastfeeding, early dairy product use, and day care exposure.^{2,48} Identifying the exact environmental exposures and interactions between those that are associated with pediatric MS will lead researchers back to the bench to unravel biological processes at play and possibly allow the development

of prevention strategies, particularly for those families with higher risk.

CONCLUSIONS

We found evidence for maternal and perinatal factors having influence on developing pediatric MS. The biological mechanisms for our observed associations remain unknown and will be a focus of future study. Of additional interest are the potential mediating roles of the microbiome in these associations and in epigenetic changes that occur in this vulnerable developmental period.

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ABBREVIATIONS

CI: confidence interval
MS: multiple sclerosis
OR: odds ratio

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Address correspondence to Jennifer S. Graves MD, PhD, MAS, 675 Nelson Rising Ln, Ste 221, Box 3206, San Francisco, CA 94158; Telephone: (415) 353-8365; Fax: (415) 514-2170; E-mail: jennifer.graves@ucsf.edu

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