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Increased Risk of Autism Spectrum Disorders in Children Born to Women With Systemic Lupus Erythematosus

Results From a Large Population-Based Cohort

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Objective. **In utero exposure to maternal antibodies and cytokines are potential risk factors for autism spectrum disorders (ASDs). The aim of this study was to determine whether children born to mothers with systemic lupus erythematosus (SLE) have an increased risk of ASD compared to children born to mothers without SLE.**

Methods. **The study population was derived from the Offspring of SLE Mothers Registry (OSLER), a large population-based cohort identified through healthcare databases in Quebec (1989–2009) comprising all women who had ≥1 hospitalization for a delivery (stillbirth or live birth) after SLE diagnosis. As general population controls, a randomly selected group of women without SLE was matched ≥4:1 to the mothers with SLE for age and year of delivery. Children born live to mothers with SLE and those born live to matched controls were identified, and a recorded diagnosis of ASD was ascertained for each child. Multivariate analyses were performed to adjust for parents' demographic characteristics, sex, birth order of the child, maternal comorbidities, and obstetric complications.**

Results. **In total, 509 women with SLE had 719 children, and 5,824 matched controls had 8,493 children. Children born to women with SLE were more frequently found to have a diagnosis of ASD compared to controls (frequency of recorded ASDs 1.4% [95% confidence interval (95% CI) 0.8–2.5] versus 0.6% [95% CI 0.5–0.8]), a difference of 0.8% (95% CI 0.1–1.9). The mean age at ASD diagnosis was younger in offspring of SLE mothers (mean 3.8 years, 95% CI 1.8–5.8) compared to offspring of controls (mean 5.7 years, 95% CI 4.9–6.5). In primary multivariate analysis, SLE offspring had a substantially increased risk of ASD compared to controls (odds ratio 2.19, 95% CI 1.09–4.39).**

Conclusion. **Compared to children from the general population, children born to women with SLE have an increased risk of ASD, although, in absolute terms, it represents a rare outcome. These hypothesis-generating data provide direction for additional studies of maternal autoimmunity and ASD risk.**

In North America, autism spectrum disorders (ASDs) affect 0.5–1% of school-age children (1,2). Systemic lupus erythematosus (SLE) is a multisystem disease that predominantly occurs in women during their childbearing years. Children born to women with SLE may have an increased risk of neurodevelopmental disorders as compared to children born to healthy women. However, the evidence is limited, being based on only a

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handful of small observational studies (3–8). Moreover, none of those studies specifically evaluated the risk of ASD.

Recent experimental data suggest that in utero exposures to maternal antibodies and cytokines are important risk factors for ASD (9,10). Interestingly, women with SLE display high levels of autoantibodies (e.g., anti–*N*-methyl-D-aspartate receptor [anti-NMDAR] antibodies) and cytokines (e.g., interleukin-6), which have been shown, in animal models, to alter fetal brain development and induce behavioral anomalies in offspring (11,12). Furthermore, patients with SLE and individuals with ASD share a common genetic predisposition to the C4B null allele, which could impair the fetal immune response to immunologic insults in utero (13–15). Moreover, pregnant women with SLE are at increased risk of adverse obstetric outcomes, such as premature birth and small for gestational age (SGA) babies. In addition, medication exposures, such as anticonvulsant agents, have been implicated as potential risk factors for ASD (16–18).

Based on the available data, and since children exposed in utero to SLE face several potential risk factors for neurodevelopmental disorders, we aimed to evaluate, in a large population-based study, whether the offspring of mothers with SLE have an increased risk of ASD compared to children born to mothers without SLE.

SUBJECTS AND METHODS

Study cohort. The study was approved by the Commission d'accès à l'information du Québec and the McGill University Research Ethics Board. Informed consent is not required for administrative database research in Quebec.

The Offspring of SLE Mothers Registry (OSLER) comprises data on a population-based cohort of 719 children born to mothers with SLE, and a matched control group of 8,493 children born to mothers without SLE. To create this large cohort, we identified all women with SLE who had ≥1 hospitalization for a delivery (either a stillbirth or a live birth) in the interval between January 1989 and December 2009, using data from the MED-ECHO database (Maintenance et exploitation des données pour l'étude de la clientèle hospitalière) and the RAMQ billing database (Régie de l'assurance maladie du Québec). MED-ECHO is an administrative database containing information on all hospitalizations in Quebec since 1987, and provides, for each hospitalization, a primary discharge diagnosis and up to 15 nonprimary diagnoses, captured as International Classification of Diseases, Ninth Revision (ICD-9) codes (and since 2006, ICD-10 codes). The RAMQ billing database records one physician-assigned diagnosis, based on ICD-9 codes, for each physician encounter.

Determination of in utero exposure to SLE. Women were identified as an SLE case (with diagnosis based on a validated definition [19], using ICD-9 code 710.0 or ICD-10 code M32) if they had any of the following: 1) ≥1 hospitalization with a diagnosis of SLE (either primary or nonprimary) prior to the delivery, 2) a diagnosis of SLE (either primary or nonprimary) recorded at the time of their hospitalization for delivery, or 3) ≥2 physician visits with a diagnosis of SLE, occurring 2 months to 2 years apart, prior to the delivery. In these same databases, a general population group of women who did not have a diagnosis of SLE prior to or at the time of delivery was identified as controls, composed of women who were matched ≥4:1 to the mothers with SLE for age and year of delivery.

Mother–child linkage was done using a specific identification number, present in every child's file in the databases; this ensured that there were very few linkage failures (<2%). Those children born live were the basis of the OSLER cohort for outcome ascertainment and long-term followup in our current study, one being the exposed group consisting of children born to women with SLE, and the other being the control group consisting of children born to women without SLE.

Ascertainment of ASD. The cohort of children was linked to determine hospitalizations and all diagnoses throughout the observation interval. This cohort interval spanned from birth to the first of the following: end of eligibility for RAMQ coverage (i.e., migration from Quebec), event of interest (i.e., ASD), age 18 years, death, or end of study (i.e., December 31, 2009). We ascertained ASD in offspring based on a previously validated definition requiring the presence of at least one relevant diagnostic code (i.e., ICD-9 code 299 or ICD-10 codes F84.0, F84.1, F84.3, F84.5, F84.8, or F84.9, which encompass the diagnostic classifications of autistic disorder, atypical autism, childhood disintegrative disorder, Asperger's syndrome, and pervasive developmental disorder not otherwise specified) in the hospitalization database or physician billing database (20).

Assessment of relevant covariates. For all mothers in our study, we reviewed the MED-ECHO and RAMQ data to identify specific preexisting and current comorbidities (i.e., pregestational diabetes, asthma, or depression) recorded in the 2 years prior to (and including) the time of delivery, as well as obstetric complications, such as preterm birth, at the time of the hospitalization for delivery. The diagnosis of specific comorbidities and obstetric complications was based on ICD-9/ICD-10 codes indicating ≥1 hospitalization or ≥2 physician visits (≥8 weeks apart) for the diagnosis of interest, in accordance with previously validated methods (21,22).

The Institut de la statistique du Québec (ISQ) provided data on the demographic characteristics of the parents at the time of delivery, including maternal education and paternal age, as well as maternal and paternal birthplace, maternal language, and language spoken at home, which were used to establish the race/ethnicity of the offspring. In addition, we obtained data on birth order, infant birth weight, and gestational age, allowing determination of babies classified as SGA (i.e., having a birth weight below the 10th percentile of Canadian statistics for gestational age [23]) and premature births (i.e., babies born before 37 weeks' gestation).

Comprehensive and valid data on drug exposures were available from the RAMQ prescription database, but only for beneficiaries of the public drug plan (24), which covers recipients of social assistance and workers and their families who do not have access to a private drug insurance program. In our cohort, 22% of children of mothers with SLE and 21% of children of controls were born to a mother with public drug coverage throughout pregnancy.

In this subgroup, we obtained all information on the prescription of certain types of medications, including corticosteroids (i.e., oral or intravenous corticosteroids), antimalarials (i.e., hydroxychloroquine or chloroquine), immunosuppressives (i.e.,

azathioprine, mycophenolate mofetil, mycophenolate sodium, and methotrexate), and any types of anticonvulsants and antidepressants. We used gestational age at birth to calculate back to the estimated start of the gestational period, and then determined whether a medication exposure of interest ever occurred during pregnancy (based on ≥1 prescription filled during gestation).

Statistical analysis. We performed univariate and multivariate analyses using the generalized estimating equation method to estimate the odds ratio (OR) for the outcome of interest (i.e., ASD) in children born to women with SLE, relative to the control group. We assessed the robustness of our effect estimates by conducting exploratory Cox proportional hazard analyses with frailties, which provided similar results. These analyses were performed using the R statistical program, version 2.15.1 (25).

In primary multivariate analysis, we matched exposed and unexposed subjects for maternal age and calendar year of delivery, but we also further adjusted for maternal age and calendar year to control for potential residual confounding by these variables. In addition, we adjusted for birth order, as well as relevant demographic factors and maternal comorbidities, including sex of the child, maternal education, child's ethnicity/race, depression, asthma, and pregestational diabetes. After considering all of these covariates in both the univariate and multivariate models, we excluded depression from the final multivariate model because this covariate was not recorded in any mothers who had a child with ASD.

As we aimed to estimate the overall effect of in utero SLE exposure on the risk of ASD, we did not adjust for obstetric complications in our primary multivariate analysis, since obstetric complications, such as gestational diabetes, preterm birth, and SGA, are potentially on the causal pathway between in utero SLE exposure and the outcome of ASD (26). Moreover, adjustment for obstetric complications might bias the SLE effect estimate if there are unmeasured common causes of obstetric complications (e.g., SGA) and ASD (27). Nevertheless, we performed a sensitivity analysis in which we further controlled for obstetric complications (i.e., gestational diabetes, preterm birth, and SGA), and compared the SLE effect estimate to the one obtained in primary multivariate analysis. If the estimates are similar, this suggests absence of substantial bias.

The subsample of mothers with public drug coverage had a reduced number of subjects, which thereby precluded a multivariate analysis. Therefore, we used descriptive statistics to assess in utero maternal medication exposures in this subset.

When outcomes are defined by ICD codes within administrative data, one must be aware that the diagnoses are not necessarily clinically confirmed. Without easy access to a gold standard for case definition, the true disease state for each subject is unknown (i.e., latent), and the sensitivity and specificity of a single diagnostic definition cannot be directly estimated. One can, however, use various case definitions in Bayesian latent class models, with each available method of case ascertainment contributing some information about the case status of each individual. With Bayesian latent class models, instead of trying to identify a disease case (or outcome) with certainty, subjects are assigned a probability of being a disease case, based on prior inputs about the sensitivity and specificity of one or more diagnostic tests and their case ascertainment data (26).

Thus, in a further sensitivity analysis, we used this approach to account for the imperfection in case ascertainment from each of our 2 methods (billing and hospitalization diagnoses). Based on a previous study assessing the validity of ASD case definitions using administrative data, we assumed a range of sensitivities and specificities for the diagnoses recorded at the time of hospitalization (sensitivity 5–45%, specificity 90–100%) and the diagnoses recorded on physician billing (sensitivity 65–95%, specificity 80–100%), each being added to the model as prior information (20). We also used less informative prior information to check the robustness of our parameter estimates. We fit a Bayesian latent class hierarchical regression model to provide estimates of ASD risk, based on the sensitivities and specificities of the case definitions. The first level of the model accounted for sampling variability in ASD risk, correlation between siblings (by adding a cluster term for each mother), and errors in the 2 case ascertainment methods. These were represented by binomial distributions, in which the probability of a positive test was adjusted for the sensitivity and specificity of each method of ascertainment. We also added a term to estimate the possible dependence of the 2 case definitions (28).

The second level of the model accounted for variations in ASD risk according to maternal demographics (age and education) and comorbidities (asthma and pregestational diabetes), sex of the child, birth order, and calendar year of delivery, which were derived from a logistic regression model on the binomial probabilities from the first level. For each parameter estimate, we calculated a 95% credible interval (95% CrI), the Bayesian analog to frequentist confidence intervals (CIs). WinBUGS (version 1.4.3; MRC Biostatistics Unit, University of Cambridge, Cambridge, UK) was used to fit these models (29).

RESULTS

In total, 509 women with SLE had 719 children, while 5,824 matched control subjects had 8,493 children. The mean ± SD maternal age of the combined cohort was 30.3 ± 5.0 years. The mean ± SD duration of SLE in mothers was 3.7 ± 4.0 years (Table 1). The demographic characteristics of the mothers with SLE were similar to those of the controls, except for race/ethnicity, in which mothers with SLE were less likely to be white. In addition, compared to controls, mothers with SLE had more comorbidities and experienced substantially more obstetric complications, such as preterm births and SGA babies. In utero drug exposures were more frequent in SLE offspring compared to control offspring, with exposures to corticosteroids and antimalarial drugs being the most common medications prescribed during SLE pregnancies.

Children born to women with SLE had more recorded ASD diagnoses compared to controls (frequency of recorded ASDs 1.4% [95% CI 0.8–2.5] versus 0.6% [95% CI 0.5–0.8]), with a difference of 0.8% (95% CI 0.1–1.9). In terms of the absolute rate of events, ASD was still a relatively infrequent occurrence, with 63 cases identified (10 among children of mothers with SLE and 53 among children of controls) over 83,753 person-years of followup, resulting in an incidence rate of 75.2 per 100,000 person-years.

Table 1. Characteristics of the study cohort*

Characteristic	SLE offspring (n = 719)	Control offspring (n = 8,493)
Maternal characteristics		
Age, mean ± SD years	30.2 ± 5.1	30.3 ± 5.0
Level of education, mean ± SD years	14.0 ± 3.1	13.8 ± 3.1
Marital status, no. (%)		
Couple	576 (80.1)	6,904 (81.3)
Single	50 (7.0)	523 (6.2)
Unknown	93 (12.9)	1,066 (12.6)
Comorbidities, no. (%)		
Hypertension	47 (6.5)	85 (1.0)
Asthma	38 (5.3)	238 (2.8)
Diabetes	23 (3.2)	144 (1.7)
Depression	11 (1.5)	34 (0.4)
Paternal characteristics		
Age, mean ± SD years	33.2 ± 5.8	33.3 ± 5.9
Offsprings' demographic characteristics		
Male sex, no. (%)	402 (55.9)	4,374 (51.5)
Ethnicity, no. (%)		
White	444 (61.8)	6,225 (73.3)
Other	275 (38.2)	2,268 (26.7)
Obstetric characteristics		
Gestational age, mean ± SD weeks	37.7 ± 2.9	38.8 ± 1.9
Birth weight, mean ± SD grams	2,976 ± 707	3,366 ± 567
Birth order, no. (%)		
1	308 (42.8)	2,333 (27.5)
≥2	411 (57.2)	6,160 (72.5)
Obstetric complications, no. (%)		
Preterm birth	157 (21.8)	637 (7.5)
Small for gestational age	120 (16.7)	694 (8.2)
Gestational diabetes	30 (4.2)	263 (3.1)
In utero exposure to medications		
Mothers with public drug coverage, no. (%)	155 (21.5)	1,770 (20.8)
Corticosteroids	34 (21.9)†	12 (0.7)‡
Antimalarials	25 (16.1)†	1 (0.1)‡
Immunosuppressives	11 (7.1)†	0 (0.0)‡
Antidepressants	11 (7.1)†	52 (2.9)‡
Anticonvulsants	1 (0.6)†	7 (0.4)‡

* In total, 509 women with systemic lupus erythematosus (SLE) had 719 children, and 5,824 matched control women had 8,493 children.
† Denominator used for proportion is the number of children born to mothers with SLE who had public drug coverage during pregnancy.
‡ Denominator used for proportion is the number of children born to matched control mothers who had public drug coverage during pregnancy.

In both groups of children, most ASD diagnoses were registered in the RAMQ billing database (Table 2), with psychiatrists most frequently recording the diagnosis (in 59% of cases). In the MED-ECHO hospitalization database, an ASD diagnosis was recorded for approximately one-fourth of the children at the time of hospitalization (Table 2). The mean age at ASD diagnosis was younger in offspring of SLE mothers (mean 3.8 years, 95% CI 1.8–5.8) than in offspring of controls (mean 5.7 years, 95% CI 4.9–6.5).

The unadjusted OR for ASD in children born to women with SLE, compared to children born to control women, was 2.25 (95% CI 1.13–4.45). In the primary multivariate analysis, children born to women with SLE had a

Table 2. Sources of a recorded ASD diagnosis among offspring of mothers with SLE and offspring of matched controls*

Database	SLE offspring (n = 10 cases)	Control offspring (n = 53 cases)
MED-ECHO only	1 (10)	3 (6)
RAMQ physician billing only	7 (70)	40 (75)
MED-ECHO and RAMQ physician billing	2 (20)	10 (19)

* Values are the number (%) of children born to mothers with systemic lupus erythematosus (SLE) or matched controls, for whom a diagnosis of autism spectrum disorder (ASD) was recorded in either the MED-ECHO database (Maintenance et exploitation des données pour l'étude de la clientèle hospitalière) or the RAMQ database (Régie de l'assurance maladie du Québec) or both.

Table 3. Univariate and multivariate analyses of the risk of ASDs in offspring of mothers with SLE compared to matched controls (n = 9,212)*

Covariate	Univariate model	Primary multivariate model	Multivariate model including obstetric complications
Maternal SLE			
No	Reference	Reference	Reference
Yes	2.25 (1.13–4.45)	2.19 (1.09–4.39)	1.97 (0.95–4.08)
Sex of child			
Female	Reference	Reference	Reference
Male	4.01 (2.13–7.56)	3.96 (2.10–7.47)	3.85 (2.03–7.30)
Birth order			
1	Reference	Reference	Reference
≥2	0.80 (0.47–1.35)	0.82 (0.47–1.44)	0.84 (0.48–1.48)
Race/ethnicity			
Other	Reference	Reference	Reference
White	1.04 (0.59–1.83)	1.06 (0.60–1.89)	1.07 (0.60–1.92)
Education level			
High school or lower	Reference	Reference	Reference
College or higher	0.76 (0.46–1.25)	0.77 (0.45–1.29)	0.82 (0.48–1.40)
Asthma			
No	Reference	Reference	Reference
Yes	1.07 (0.26–4.39)	1.10 (0.26–4.61)	1.09 (0.26–4.62)
Pregestational diabetes			
No	Reference	Reference	Reference
Yes	0.88 (0.12–6.47)	0.83 (0.11–6.26)	0.89 (0.12–6.71)
Gestational diabetes			
No	Reference	–	Reference
Yes	2.61 (1.03–6.62)		2.42 (0.93–6.26)
Preterm birth			
No	Reference	–	Reference
Yes	1.40 (0.64–3.08)		1.12 (0.49–2.55)
Small for gestational age			
No	Reference	–	Reference
Yes	2.00 (1.01–3.96)		1.69 (0.84–3.43)

* Values are the odds ratio (95% confidence interval) for the risk of autism spectrum disorders (ASDs) in children born to mothers with systemic lupus erythematosus (SLE) relative to children born to control mothers without SLE, matched for age and calendar year of delivery.

substantially increased risk of ASD compared to controls (OR 2.19, 95% CI 1.09–4.39). In the sensitivity analysis in which we further adjusted for the obstetric complications of gestational diabetes, preterm birth, and SGA, the SLE effect estimate remained similar (OR 1.97, 95% CI 0.95–4.08), although the 95% CI included the null value (Table 3).

In addition to maternal SLE, other potential predictors of ASD in the adjusted multivariate analysis included gestational diabetes (OR 2.42, 95% CI 0.93–6.26) and SGA (OR 1.69, 95% CI 0.84–3.43), although wide confidence intervals precluded definitive conclusions about these variables. Of note, male sex was a strong predictor of ASD in the multivariate analyses (primary analysis OR 3.96, 95% CI 2.10–7.47).

In the subsample of children of mothers with public drug coverage (including 155 SLE offspring and 1,770 control offspring), in utero medication exposures were rare in the 18 ASD cases (2 born to SLE mothers and 16 born to control mothers). None of the 18 ASD cases were exposed to antimalarials, antidepressants, or immunosuppressants in utero. Only 1 case (born to a mother with SLE) was exposed to corticosteroids, and another case (born to a control mother) was exposed to anticonvulsants.

In Bayesian latent class analyses, in which we accounted for all sources of uncertainty about case ascertainment, the unadjusted effect estimate of SLE (OR 2.67, 95% CrI 0.98–6.47) and the adjusted effect estimate of SLE (OR 2.47, 95% CrI 0.88–6.07) on the risk of ASD were each similar to the estimates from the primary analysis, although the credible intervals overlapped with the null value.

DISCUSSION

Within this population, the largest cohort of SLE offspring ever assembled, we observed that children born

to mothers with SLE had a more than 2-fold increase in the risk of ASD. We also demonstrated that the effect of maternal SLE on the risk of ASD was potentially independent of obstetric complications.

There was a trend toward younger age at ASD diagnosis in offspring of mothers with SLE compared to offspring of controls, although the small number of events limited accuracy of this estimate. Nevertheless, this raises concerns as to whether there might be a different clinical presentation of ASD in children born to mothers with SLE (e.g., an earlier and/or more severe disease presentation) compared to control children. An alternative explanation might be that mothers with SLE initiate earlier consultations with healthcare professionals, because they either fear that the disease might have affected their child during pregnancy or have more frequent contacts with the healthcare system. However, in a recent study from our group within the same cohort of children, the mean age at the time of diagnosis of attention deficit hyperactivity disorder was substantially older in offspring of mothers with SLE (mean 12.5 years, 95% CI 11.7–13.3) compared to controls (mean 7.8 years, 95% CI 7.5–8.1) (30). Those findings suggest that mothers with SLE may not always consult with healthcare professionals more promptly than control mothers, and might potentially point toward a different ASD phenotype in SLE offspring.

Obstetric complications are recognized risk factors for ASD. In the present study, the direction and magnitude of the effect estimates observed for obstetric complications, including gestational diabetes and SGA, as independent predictors of ASD were in accordance with findings from prior population-based studies (17,31,32). However, due to the limited number of events, the confidence intervals associated with these effect estimates included the null value. We also observed that male sex was associated with a 4-fold increase in the risk of ASD, a finding that is consistent with that reported in published literature (2).

Administrative databases in Quebec contain information on all deliveries performed in the province of ~8 million residents, providing enough power to assess a rare event such as ASD, and allowing us to appropriately control for obstetric complications. In addition, Quebec's administrative databases are a valid data source for observational studies of SLE subjects, with prior work from our group showing that our SLE case definition has a very high specificity (0.99) (19). Of note, 16% of the children of mothers with SLE were exposed in utero to antimalarial drugs, which is comparable to the previously reported rate of exposure in SLE pregnancies observed over a similar time period in a well-established cohort of lupus patients in a tertiary care setting, in which 22% of mothers with lupus were exposed to antimalarial agents beyond the first trimester (33). Furthermore, a recent study evaluated the validity of obstetric variables recorded in the RAMQ, MED-ECHO, and ISQ databases, such as birth weight, gestational age, and live births, and showed very high sensitivity (0.97–0.99) and specificity (0.92–0.98) for all of the variables examined (34), thereby confirming that these administrative databases are a valid data source for obstetric variables.

Moreover, we used an ASD case definition that showed high specificity in our Bayesian latent class analyses (specificity of at least 99.7%, 95% CrI 99.5–99.9). Thus, it is unlikely that a substantial fraction of subjects without a clinically confirmed ASD diagnosis were identified as ASD cases in our study. We nevertheless accounted for imperfect case ascertainment in Bayesian latent class models, which provided estimates that still pointed toward a potentially increased risk of ASD in SLE offspring.

Our study has potential limitations. First, we only had information on in utero drug exposures in the subsample of children whose mothers had public drug coverage throughout pregnancy, representing ~20% of the entire cohort. Although medication exposures were rare in ASD cases within this subsample, we cannot definitively conclude that the effect of SLE on the risk of ASD is completely independent of the medications being administered to mothers during pregnancy.

Furthermore, in all observational studies, unmeasured (or poorly measured) confounding always represents a concern. We have considered this and used well-defined proxies for certain variables (e.g., race/ethnicity). Still, administrative databases do not contain information on, for example, smoking and obesity, which have been associated with a slightly increased risk of having a child with ASD in exposed pregnant women (31,35). However, prior data from Quebec suggest that smoking practices and the prevalence of obesity in SLE patients are comparable to those in the general population (36). Therefore, the lack of information on smoking and obesity is unlikely to have introduced substantial bias.

Administrative databases in Quebec do not record serologic data on any individual. This would have been of interest, particularly in women with SLE, to determine whether specific types of maternal autoantibodies, such as anti-DNA antibodies (a subset of which are anti-NMDAR antibodies), could be predictive of ASD in children born to women with SLE (11). Nevertheless, establishing an association between in utero exposure to SLE and ASD may shed new light on the potential role of maternal autoantibodies in the pathogenesis of ASD.

In summary, compared to children from the general population, children born to mothers with SLE appear to have a more than 2-fold increase in the risk of ASD. The effect of maternal SLE on the risk of ASD is potentially independent of obstetric complications. Our study findings should prompt future research, notably on the role of maternal SLE-related autoantibodies, which could yield important insights into the physiopathology of these complex disorders.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Vinet had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Vinet, Pineau, Clarke, Scott, Fombonne, Joseph, Platt, Bernatsky.

Acquisition of data. Vinet, Bernatsky.

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