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Asthma in children of mothers with systemic lupus erythematosus and the role of preterm birth

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Abstract

Objective—Systemic lupus erythematosus (SLE) and asthma share inheritable IgE-related pathophysiology, but the association between maternal SLE and asthma in the offspring has not been explored. Our aim was to investigate the association between maternal SLE during pregnancy and childhood asthma and examine the role of preterm birth as a mediator of the association using Swedish register data.

Methods—Information on 12000 singleton live births (2001–2013) was collected from the Medical Birth Register. Childhood asthma was defined as at least one ICD-coded visit in the National Patient Register. Prevalent maternal SLE at delivery was identified from the Medical Birth Register and the National Patient Register. Risk ratios (RRs) for asthma were estimated while controlling for confounders. Mediation analysis was used to estimate what percentage of the total effect can be explained by preterm birth (defined as either <34 or <37 weeks' gestation).

Results—We compared 775 children born to mothers with SLE with 11225 born to mothers without SLE. Ninety seven (13%) children of mothers with SLE were diagnosed with asthma compared to 1211 in the unexposed group (11%). The risk ratio for childhood asthma was 1.46 (95% CI 1.16–1.84). In mediation analysis, 20 to 29% of the total effect of SLE was explained by preterm birth.

Conclusion—Prevalent maternal SLE during pregnancy is associated with an increased risk of asthma in the offspring. While preterm birth can explain a fair proportion of this association, additional unidentified mechanisms are also likely to play a role.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that presents most commonly in women of childbearing age. Recently, experimental studies confirmed that autoreactive antibodies of the IgE subclass, which are found in high concentrations in SLE patients, are implicated in the pathogenesis of SLE and its manifestations (1, 2). Similar IgE-

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Author contributions

Study conception: MR, CN, JFS. Statistical analysis: MR. Data interpretation: MR, CN, EVA and JFS. Drafting of article: MR, JFS. Critical revision of article: MR, CN, EVA and JFS. Final approval of article: MR, CN, EVA and JFS.

mediated (atopic) mechanisms, with a strong genetic component, are involved in the development of asthma, irrespective of SLE status.

It is hypothesized that IgE-mediated mechanisms involved in the expression of SLE in the mother may also be implicated, to a degree, in asthma development in the offspring. However, preterm birth, defined as <37 completed gestational weeks, may fully or partially explain any potential association between maternal SLE and childhood asthma. Preterm birth, especially moderate preterm (defined as <34 weeks' gestation), disrupts lung maturation, and is a recognized independent risk factor for asthma development later in childhood (3). Preterm delivery is about four times more frequent in SLE pregnancies compared to general population pregnancies in Sweden (4). In fact, estimates for preterm delivery range from 20 to 40%, a variation owing to SLE severity and complications (4, 5).

To our knowledge, the association between maternal SLE and asthma development in the offspring has not been adequately investigated. One published study indicated a higher prevalence of asthma and IgE levels in the serum of children born to mothers with SLE compared to controls (6), and a second study reported more allergic conditions in the children of women with SLE using healthcare databases from Quebec (7). Whether this was driven by preterm birth is unclear. We used Swedish registers to establish a cohort of children born from 2001 to 2013 to study the association between maternal SLE and asthma development in the offspring and the potential effect of preterm birth as a mediator of this association.

PATIENTS AND METHODS

Study setting and sources

In Sweden, access to health care is universal and permanent residents obtain personal identification numbers that allow the linkage of their records in registers. In addition to all live births, the Medical Birth Register (MBR) includes data on stillbirths from 28 gestational weeks until 2008 and as early as 22 weeks' gestation thereafter. Hospitalization information (national coverage from 1987) and non-primary care/outpatient visits in public and some private practices (nationwide since 2001) are registered in the National Patient Register (NPR). Starting from July 2005, information on all dispensed prescriptions is captured in the Prescribed Drug Register (PDR).

Study population

In this cohort study, we used data from a unique, large and population-based cohort, the Swedish Lupus Linkage (SLINK). Detailed information on this linkage is published elsewhere (8). Briefly, it includes individuals with SLE identified from the NPR and up to five individually matched (on birth year, sex and residential county) comparators from the general population. Our study population was composed of singletons born to women from SLINK between January 2001 and December 2013. Ethical approval was provided by the Regional Ethics Board in Stockholm (DNR 2011/920-31/1).

Childhood asthma

We used two definitions, the second being stricter to minimize potential misclassification. The primary asthma definition was at least one ICD-coded outpatient or inpatient visit in the NPR (ICD-10 J45–J46). The date of the first asthma visit served as a proxy for the date of diagnosis. The secondary asthma definition was assessed in a subset of the children born 2006 and onwards and required at least two prescription dispensations for asthma medications in the PDR (inhaled β 2-agonists [ATC code R03AC], corticosteroids [R03BA] or fixed combinations [R03AK], leukotriene receptor antagonists [R03DC], or omalizumab [R03DX05]) in addition to at least one asthma visit in the NPR. The earliest date of either the asthma visit in NPR or dispensation was regarded as the date of diagnosis. Children were followed until diagnosis of asthma, first emigration (date obtained from the Total Population Register), death (date retrieved from the Cause of Death Register), or the end of the study (December 31, 2013), whichever occurred first.

Prevalent SLE at delivery

We compared children born to mothers with prevalent SLE at delivery to those without. Prevalent SLE at delivery was identified in either the NPR or the MBR. In the NPR, SLE was defined as at least two inpatient or outpatient visits (ICD-10 M32, ICD-9 710A, ICD-8 734.10) with at least one in a specialized clinic (rheumatology, internal medicine, nephrology, or dermatology). The offspring was considered born to a mother with SLE if maternal SLE was identified before the date of delivery. In the MBR, we searched maternal and pregnancy diagnoses for a mention of SLE using the same ICD codes. Drug-induced lupus (ICD-10 M32.0) identified in either register was excluded from the definition of SLE.

Other variables

Additional data from the MBR included: maternal age at delivery and country of birth (grouped in Nordic and non-Nordic), offspring's date of birth, parity (first or subsequent birth), self-reported maternal first trimester smoking (yes/no), sex of offspring, gestational age in weeks, preterm and moderate preterm birth (<37 and <34 gestational weeks, respectively; yes/no). Maternal height and weight measured at the first prenatal visit were used to identify obese mothers according to WHO (body mass index ≥ 30.0 kg/m²). Attained tertiary education at delivery (yes/no) was retrieved from the Education Register.

We defined maternal asthma history as at least one asthma ICD code prior to the date of delivery in the NPR (ICD-10 J45–J46, ICD-9/8 493). As a proxy for SLE activity during the first two trimesters of pregnancy, we used at least two dispensations in the PDR of systemic corticosteroids (methylprednisolone [ATC code H02AB04], prednisolone [H02AB06], prednisone [H02AB07], and hydrocortisone [H02AB09]) and azathioprine (L04AX01). Data were available for deliveries starting April 1, 2006 allowing for nine months after the PDR started.

Statistical analysis

To compare the risk of asthma between children born to mothers with and without SLE at delivery, we estimated risk ratios (RRs) and corresponding 95% confidence intervals (CIs) using a modified Poisson regression model accounting for mother-offspring clustering. The

model was also adjusted for the following confounding, maternal variables: age at delivery (continuous), tertiary education (yes/no), obesity (yes/no), self-reported first trimester smoking (yes/no), and history of asthma (yes/no). Based on previous literature on the association between pregnancy factors and childhood asthma, we stratified our analysis by four factors: sex of the offspring, maternal first trimester smoking, preterm birth (<37 and <34 weeks' gestation), and parity (first or subsequent birth). All analyses were repeated for the stricter childhood asthma definition in a subset of the study population. In a sensitivity analysis, we reran the models after imputing missing data for smoking, assuming mothers with missing smoking status were first smokers and then non-smokers.

We conducted mediation analyses using a causal inference counterfactual approach (9) to examine whether and in what proportion the association between maternal SLE and childhood asthma could be explained by preterm birth. The analysis was stratified by parity to disentangle the complex interplay between maternal SLE, preterm delivery, and childhood asthma. Total effects were decomposed into natural direct (NDE) and indirect effects (NIE; via preterm birth) and reported on the risk ratio scale. They were estimated by two modified Poisson regression models to account for autocorrelation when necessary. Based on prior knowledge, maternal age (continuous), tertiary education (yes/no), obesity (yes/no), first trimester smoking (yes/no), and asthma history were added to the models to account for exposure-mediator, mediator-outcome and exposure-outcome confounding. An exposure-mediator interaction term was omitted from the models because it was not statistically significant. The proportion mediated through preterm birth was calculated using the formula

$$\left[\frac{RR_{NDE}(RR_{NIE} - 1)}{RR_{NDE} \times RR_{NIE} - 1} \right] \times 100 \quad (10).$$

All data management and analyses were performed using SAS version 9.4. Missing data were included in all analyses as an additional category, unless otherwise stated.

RESULTS

Baseline characteristics of mothers and offspring

A total of 12000 children born to 7674 mothers between 2001 and 2013 in Sweden were included in this study (Table 1). Of those, 775 were the offspring of mothers with SLE diagnosed before delivery. Offspring of mothers with SLE at delivery were four to five times more likely to be born preterm (<37 weeks' gestation; 17.3% of SLE pregnancies) or moderate preterm (<34 weeks' gestation; 6.1% of SLE pregnancies) compared to those without a mother with SLE. On average, the prevalence of obesity, first trimester smoking and history of asthma were similar between mothers with and without SLE.

Risk of childhood asthma

Ninety seven (13%) children born to mothers with SLE were diagnosed with asthma (median follow-up 5.9 years [IQR 3.2–9.0]) compared to 1211 (11%) children born to mothers without SLE (median follow-up 7.4 years [IQR 4.4–10.1]; Table 2). Asthma among children whose mothers had SLE during pregnancy occurred at a rate nearly 1.5 times that of children whose mothers did not have SLE after adjusting for maternal age, tertiary

education, obesity and first trimester smoking, and maternal asthma history (RR 1.46, 95% CI 1.16–1.84).

The risk for childhood asthma was greater for children born to smoking mothers (RR 2.57, 95% CI 1.32–4.99), children born moderately preterm or preterm (RR 1.91, 95% CI 0.94–3.86 and RR 1.68, 95% CI 1.09–2.61, respectively), and first born children (RR 1.62, 95% CI 1.18–2.23). The association between maternal SLE and childhood asthma did not differ by offspring sex. Despite the restricted sample size, these findings generally persisted when we used a stricter asthma definition in a subset of the study population (Table 2). The results remained robust in sensitivity analyses accounting for missing information on maternal smoking (data not shown).

The role of preterm birth

Considering all births, 29% of the association between maternal SLE and childhood asthma was mediated by preterm birth (Table 3). The proportion was 10% lower using <34 weeks' gestation to define preterm. Stratification for parity showed that, irrespective of preterm definition, direct and total effects were stronger for first compared to subsequent birth while effects via preterm birth (indirect) were similar.

DISCUSSION

To our knowledge, this is the first study to investigate the association between prevalent maternal SLE at the time of pregnancy and asthma development in the child taking into account significant confounders and the mediating effect of preterm birth. By using a large cohort of Swedish children-mother pairs, we have shown that the rate of developing asthma is 46% higher in children born to mothers with SLE compared to mothers without SLE.

As the body of literature on the association between SLE and asthma in the offspring is limited, the results of our study can be indirectly compared to only a few studies. Sasai K. et al. indicated that the prevalence of asthma in children born to mothers with SLE was higher than controls (28% vs. 9%) and that IgE titers in the serum of children having a mother with SLE were again greater than controls in a sample of 36 patients (6). In a study from Quebec, a higher prevalence of allergic asthma in children born to mothers with SLE compared to non-SLE was reported using universal healthcare databases (7).

Maternal smoking during pregnancy was the strongest effect modifier. Our findings suggest that children born to mothers with SLE that smoke during pregnancy have the highest risk of developing childhood asthma. Smoking is a recognized risk factor for SLE, is positively associated with disease activity (11), and is a risk factor for preterm birth (12). Therefore, the increased risk for childhood asthma observed in offspring of smoking SLE mothers, is possibly explained (at least partly) by smoking's influence on SLE disease activity and premature delivery. In addition, the association was stronger for first-born compared to subsequent-born children. Such a pattern was shown for other outcomes (13) but the mechanisms remain to be clarified.

The results of the mediation analysis showed that, depending on the classification for preterm birth used, 20 to 29% of the association between maternal SLE and childhood asthma could be explained by preterm birth. While preterm birth proved to be a significant factor (mediating approximately one-third of the association), the mediation analysis indicated that the effect could be through other undetermined pathways. The mediating effect of preterm birth was attenuated by approximately 10% when we set the cutpoint to 34 weeks' gestation to account for lung prematurity, an independent risk factor for asthma. This finding suggests that the more premature the delivery, the more complex the interplay amongst factors is and single factors may have a lower impact on the association.

Our study has some limitations. Register-derived definitions of exposure and outcome might be prone to misclassification. For our primary (and liberal) definition of childhood asthma, a validation study found positive predictive values of 78–89% (depending on child's age) when tested against a doctor's diagnosis using criteria established by the Swedish Pediatric Society (14). Despite the restricted sample size, the association remained robust, if not strengthened, when we expanded our asthma definition to include dispensation of at least two asthma treatments, a definition yielding a positive predictive value of 99% (14).

Similarly, we cannot exclude the possibility of misclassification of maternal SLE. Our group found little misclassification of this definition compared with approximately 1000 clinically-confirmed cases and these data have demonstrated face validity when compared with other population-based register definitions with corresponding validation studies (15). Little data are available in these registers to examine SLE disease activity and severity and its role on the association with childhood asthma. Moreover, we missed information on maternal BMI and smoking status for about 10% of the pregnancies. However, missing data were not associated with maternal SLE and sensitivity analyses indicated that our findings were robust. Last, in the mediation analyses we omitted an exposure-mediator interaction term that was found not statistically significant. We cannot exclude the possibility, however, that the models were not well-powered to identify such interaction. In the presence of exposure-mediator interaction, we would have expected a higher proportion of the association mediated through preterm birth due to stronger natural indirect effects (and consequently weakened direct effects).

There are also several strengths. A large, nationwide and population-based sample was used to study the association between maternal SLE and asthma development in the offspring. To date, this is likely the first to have used mediation analysis to investigate whether preterm delivery is a mediator in the pathway from maternal SLE during pregnancy to asthma occurrence in the child. Moreover, because of the rich information recorded in the MBR and relatively little missing data, we could account for a number of confounding factors, and investigate potential effect modification, as well as account for birth order.

To conclude, using over one decade of data representative of nearly the entire population of Sweden, our study shows that maternal SLE during pregnancy was associated with an increased risk of asthma in the offspring, with children born to mothers with SLE who smoked during pregnancy having the greatest risk. We also found that approximately 30% of this risk was mediated by preterm delivery. However, the majority of the association between

maternal SLE and childhood asthma remained unexplained, suggesting an additional role of, to date, undetermined pathophysiologic mechanisms.

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Significance and Innovations

- IgE-related mechanisms were recently implicated in systemic lupus erythematosus (SLE) but are well-known in inheritable, atopic diseases like asthma. Preterm birth is a known risk factor for childhood asthma and occurs in a relatively large proportion of SLE pregnancies.
- This cohort study is the largest and most comprehensive investigation of the risk of childhood asthma in the offspring of mothers with SLE during pregnancy and the role of preterm birth on this association.
- Maternal SLE during pregnancy is associated with a modest increase in the rate of asthma in offspring. Children born to mothers with SLE who smoked during pregnancy have the greatest risk.
- Preterm birth can only explain up to 29% of this association.

Table 1

Characteristics of mothers and children born to mothers with and without prevalent systemic lupus erythematosus (SLE) at delivery.

	SLE pregnancy	
	Yes (n=775)	No (n=11225)
Maternal age at delivery, mean $\pm$ SD years	31 $\pm$ 4.7	31 $\pm$ 4.9
Mother born in non-Nordic country	12.1	13.6
Maternal tertiary education *	56.5	53.2
Maternal obesity at first prenatal visit *	8.5	10.0
Maternal first trimester smoking *	5.8	7.8
Maternal history of asthma	3.9	2.8
Systemic corticosteroid use during pregnancy †	27.9	0.2
Azathioprine use during pregnancy †	14.2	0.1
First birth	45.8	42.2
Female offspring	51.5	47.6
Gestational age, mean $\pm$ SD completed weeks	38 $\pm$ 2.9	39 $\pm$ 1.8
Preterm birth (<37 weeks' gestation)	17.3	4.6
Moderate preterm birth (<34 weeks' gestation)	6.1	1.2

Data are percentage including missing unless indicated otherwise.

* No. missing, SLE/non-SLE pregnancies: tertiary education 5/118; maternal obesity 81/1189; first trimester smoking 44/541.

† Two item dispensations during 1st and 2nd trimesters of pregnancy for deliveries starting April 1, 2006 (SLE n=501, non-SLE n=5947). Systemic corticosteroids include methylprednisolone, prednisolone, prednisone, and hydrocortisone.

Table 2

Overall and stratified adjusted risk ratios for asthma in children born to mothers with prevalent systemic lupus erythematosus (SLE) compared to mothers without SLE at delivery using two definitions for childhood asthma.

	Liberal childhood asthma definition [*]			Strict childhood asthma definition [†]		
	Maternal SLE, N cases/N total (%)	Non-SLE, N cases/N total (%)	Adjusted RR (95% CI) [‡]	Maternal SLE, N cases/N total (%)	Non-SLE, N cases/N total (%)	Adjusted RR (95% CI) [‡]
Overall	97/775 (13)	1211/11225 (11)	1.46 (1.16–1.84)	55/519 (11)	517/6228 (8)	1.50 (1.12–2.02)
Sex of offspring						
Female	43/399 (11)	465/5343 (9)	1.50 (1.07–2.09)	25/281 (9)	193/2980 (6)	1.51 (0.98–2.32)
Male	54/376 (14)	746/5882 (13)	1.38 (1.04–1.85)	30/238 (13)	324/3248 (10)	1.55 (1.05–2.27)
Maternal first trimester smoking [§]						
Yes	12/45 (27)	124/877 (14)	2.57 (1.32–4.99)	6/21 (29)	47/383 (12)	3.38 (1.32–8.60)
No	75/686 (11)	1039/9807 (11)	1.28 (0.98–1.66)	43/470 (9)	453/5594 (8)	1.26 (0.90–1.76)
Gestational age						
Preterm, <34 weeks	13/47 (28)	28/139 (20)	1.91 (0.94–3.86)	13/47 (28)	28/139 (20)	2.10 (0.70–6.33)
Preterm, <37 weeks	32/134 (24)	88/512 (17)	1.68 (1.09–2.61)	22/90 (24)	40/268 (15)	1.75 (1.01–3.04)
Term, ≥37 weeks	65/641 (10)	1123/10713 (10)	1.19 (0.90–1.58)	33/429 (8)	477/5960 (8)	1.06 (0.72–1.56)
Parity						
First birth	45/355 (13)	469/4732 (10)	1.62 (1.18–2.23)	28/242 (12)	195/2577 (8)	1.82 (1.21–2.74)
Subsequent birth	52/420 (12)	742/6493 (11)	1.28 (0.95–1.73)	27/277 (10)	322/3651 (9)	1.29 (0.86–1.94)

RR = risk ratio; CI = confidence interval.

^{*} Defined as 1 visit for asthma in the National Patient Register (2001–2013).

[†] Defined as 1 visit for asthma in the National Patient Register and 2 dispensations of asthma medications in the Prescribed Drug Register (2006–2013).

[‡] Adjusted for maternal age at delivery (continuous), maternal obesity (yes/no/missing), maternal tertiary education (yes/no), maternal first-trimester smoking (yes/no/missing), and maternal history of asthma (yes/no).

[§] Missing category excluded from stratifications since models did not converge.

^{||} Not adjusted for maternal history of asthma due model convergence problems.

Table 3

Estimates of direct effect and effect mediated through preterm birth of the association between maternal systemic lupus erythematosus (SLE) and asthma in children stratified by parity.

	RR (95% CI) [*]			
Mediator: Preterm birth	Direct effect	Indirect effect through preterm birth	Total effect	Proportion mediated through preterm birth
<34 weeks' gestation				
First birth	1.51 (1.11–2.06)	1.09 (1.02–1.18)	1.65 (1.21–2.25)	21%
Subsequent birth	1.22 (0.92–1.61)	1.04 (1.00–1.08)	1.26 (0.95–1.68)	18%
All	1.32 (1.07–1.63)	1.06 (1.02–1.10)	1.40 (1.14–1.73)	20%
<37 weeks' gestation				
First birth	1.46 (1.07–1.99)	1.10 (1.03–1.16)	1.60 (1.17–2.17)	23%
Subsequent birth	1.16 (0.87–1.54)	1.08 (1.03–1.13)	1.25 (0.94–1.66)	36%
All	1.26 (1.03–1.56)	1.09 (1.05–1.13)	1.37 (1.12–1.69)	29%

RR = risk ratio; CI = confidence interval.

* SLE vs. non-SLE pregnancy. Models were adjusted for maternal age at delivery (continuous), maternal obesity (yes/no/missing), maternal tertiary education (yes/no), maternal first trimester smoking (yes/no/missing), maternal history of asthma (yes/no), and autocorrelation for all/subsequent births.