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Infections in Infants Born To Mothers With Systemic Lupus Erythematosus and The Role Of Preterm Birth

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Title: Infections in Infants Born To Mothers With Systemic Lupus Erythematosus and The Role Of Preterm Birth

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Running title: Infections in infants born to women with SLE

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ABSTRACT

Objectives:

To investigate infection risk in systemic lupus erythematosus (SLE) offspring compared to non-SLE offspring, and examine the mediating role of preterm birth.

Methods:

Liveborn singletons born to mothers with SLE and general population comparators were identified in the Medical Birth Register (MBR; 2006-2021). SLE was defined by ≥2 ICD-coded visits in the National Patient Register (NPR) and MBR, with ≥1 visit before pregnancy. Infection was defined as any ICD-coded visit in the NPR or anti-infectives in the Prescribed Drug Register. Modified Poisson regression models estimated risk ratios and 95% confidence intervals (RR; 95%CI) of infection associated with maternal SLE adjusted for maternal age, first-trimester smoking, and calendar year. Causal mediation analysis estimated the percentage of the total effect explained by preterm birth.

Results:

Twenty-six of 1,248 (2.1%) SLE offspring and 414 of 34,886 (1.2%) non-SLE offspring had an infection in the first 72 hours with a corresponding RR of 1.62 [95%CI 1.09-2.42]. In the first year of life, risk of infection was higher in SLE offspring than in non-SLE offspring (38.2% vs. 37.2%; RR 1.09 (95%CI 1.01-1.17). The percentage of the total effect of maternal SLE on infant infection mediated through preterm birth was 86% for infection in the first 72 hours and 27% in the first year of life.

Conclusions:

The risk of infection in SLE offspring is most increased in the first three days after birth, with a 62% higher risk of infection compared to non-SLE. The majority of this association can be explained by preterm birth.

Strengths and limitations of this study

- The use of prospectively collected, contemporary, population-based data from the entire Swedish population minimized selection bias and increased power.
- We were able to link infants to mothers with and without SLE and follow them for one year after birth by using each individual's unique personal identification number.
- Mothers with SLE might seek and/or receive more healthcare than mothers without SLE which would result in an overestimate of the association between maternal SLE and infant infection.
- The national registers used in this study do not capture information on lupus disease activity, clinical phenotype or, severity which might modify the risk of infant infection.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory autoimmune disease that predominantly affects women of childbearing age. Women with SLE have a 20-30% risk of preterm delivery which is two to three times higher than the risk among women without SLE.(1-5) The downstream effect of maternal SLE on infants is not as clear. A previous study from Sweden reported that 21% of infants born to women with SLE had an infection during their first year of life compared to 14% of infants born to mothers without SLE.(4) As the nature of this study was strictly descriptive, it remains unclear if the association between maternal SLE exposure during pregnancy and infections in infants is still present after considering important confounding factors and the mediating effect of preterm birth.

Preterm delivery (delivery before 37 weeks of gestation), is likely an important mediator in the association between maternal SLE and infant infections. Being born preterm is a risk factor for infections, especially early-onset infections of which clinical manifestations usually appear within the first 72 hours.(6, 7) This is partly due to maternal infection (one cause of preterm birth) and immature organs (e.g. lungs and skin). Also, preterm infants often require prolonged intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms, placing them at increased risk for infections. (6, 7) Infants born preterm have on average 1.5 times the total number of infections in the first year of life compared to infants born full-term.(8)

The current study investigates the association between maternal SLE and the risk of infections in infants in the first year of life, and how much of the association can be explained by preterm birth. We used nationwide population-based registers in Sweden to compare infection risk in infants born to women with SLE to infants born to women without SLE.

METHODS

Study setting and sources

In Sweden, access to health care is universal and residents have a unique personal identification number that allows for the linkage of their records in registers. Maternal health during pregnancy, delivery, and neonatal outcomes of over 98% of deliveries in Sweden are registered in the Medical Birth Register (MBR) starting in 1973. Until July 2008, births ≥28 gestational weeks and live births were included. From July 2008, the MBR also included stillbirths ≥22 gestational weeks. Information on sex, year of birth, county of residence, and immigration, from 1968 onward was captured in the Total Population Register (TPR). Date of death is collected in the Cause of Death Register. Hospitalization data with national coverage from 1987 onward and non-primary care specialized outpatient visits since 2001 are captured in the National Patient Register (NPR). Primary and secondary diagnoses are listed for each visit using International Classification of Diseases (ICD) codes. Since July 2005, dispensed prescriptions of medications in the Swedish population are captured in the Prescribed Drug Register (PDR) using Anatomical Therapeutic Chemical (ATC) codes.

Study population

Infants born to mothers with SLE (exposed) and without SLE from the general population (unexposed) were identified by linking the NPR to the MBR. Women with ≥2 ICD-coded visits for SLE (ICD-10: M32, excluding M32.0 drug-induced lupus) in the inpatient or outpatient records of the NPR and matched to ten randomly sampled comparators from the general population without SLE, identified in the TPR, on year of birth, sex, calendar time, and county of residence. From this population, we identified mothers who gave birth to a liveborn singleton registered in the MBR between March 2006 (as the PDR started in July 2005) and December 2021.

Maternal SLE at delivery

The infants were considered to be born to a mother with SLE if the mother had at least two discharge codes of SLE from in- or outpatient records of the NPR and/or MBR before or during pregnancy. At least one of these discharge codes was required to occur before pregnancy and be given at a department or specialist that diagnoses, treats or manages SLE (rheumatology, dermatology, nephrology, internal medicine and/or paediatrics). The first observed SLE discharge code was used as a proxy for

diagnosis date. Infants born to women with only one visit for SLE before delivery or with no visits with a specialist were excluded.

The study period was from the infant's date of birth for one year, death, or emigration, whichever came first. Ethical approval was granted by the Regional Ethics Review Board in Stockholm (DNR 2021-01148).

Infections in infants

Any infant infection was identified using both primary and secondary ICD-coded visits in the inpatient and outpatient records of the NPR and dispensed prescriptions of anti-infectives in the PDR (the majority of which were antibiotics). We also examined hospitalized infections separately, defined as a hospitalization listing infection as the primary diagnosis in the inpatient records of the NPR. The first infection during follow-up was categorized into upper respiratory, lower respiratory, gastrointestinal, and other infections. For a list of ICD codes for infections and ATC codes for dispensed prescriptions of anti-infectives, see Supplementary Table 1, adapted from Sørup et al. (2016), Miller et al. (2016) and Bröms et al. (2020).(10-12) For any infection and hospitalized infection, we identified those occurring in the first three days (early-onset), within one month and within one year of birth.

Preterm delivery and other covariates

Preterm birth (delivery before 37 weeks of gestation) and very preterm birth (delivery before 32 weeks of gestation) were identified in the MBR. Additional data from the MBR included the infant's sex, infant's date of birth, parity (first or subsequent birth), gestational age in weeks, maternal age at delivery, and self-reported maternal first trimester smoking (yes/no/missing). Maternal height and weight collected at the first prenatal visit was used to calculate the body mass index (BMI) as weight divided by height squared (kg/m^2). Maternal infection during pregnancy was collected from the NPR and defined as an inpatient or outpatient visit listing an ICD code for infection.

Statistical analysis

Continuous variables were described using means and standard deviations (SD) and categorical variables were described with frequencies and column percentages. We calculated risk ratios (RR) and corresponding 95% confidence intervals using modified Poisson regression models to estimate the risk of infant infection comparing infants born to mothers with SLE to infants born to general population comparators.(13) RRs

were estimated for any infection and hospitalized infection within the first 72 hours, within the first month and within the first year of life in infants, overall and by preterm birth. Models were adjusted for maternal age at delivery (continuous), maternal fist-trimester smoking (yes/no/missing), and calendar year (continuous). In a sensitivity analysis, we reran all models among only first births. It has been shown that outcomes from the first pregnancy might be less favorable than subsequent pregnancies.(16)

We conducted a mediation analysis using a casual inference counterfactual approach to examine how much of the association between maternal SLE and any infection in infants could be explained by preterm birth.(14) The mediator was preterm birth (<37 weeks of gestation) compared to full term birth. Total effects were separated into natural direct effects and natural indirect effects through preterm birth. Results were reported on the odds ratio scale which estimates the RR and is very comparable with the RR. Based on knowledge from the literature, causal mediation models were adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous) to account for exposure-mediator, mediator-outcome, and exposure-outcome confounding.(15) We included an interaction between maternal SLE and preterm birth in the model. Because maternal infection is associated with both preterm birth and infant infection, we also performed a sensitivity analysis excluding mothers with an infection during pregnancy in a sensitivity analysis. All data management and analyses were performed using SAS, version 9.4.

RESULTS

Baseline characteristics of mothers and infants. We included 1,248 infants born to mothers with SLE and 34,886 infants born to general population comparators (Table 1). The proportion of births that were first born was higher among SLE-exposed infants compared to those infants born to mothers without SLE (44.7% versus 40.9%), and SLE-exposed infants were almost three times more likely to be born preterm (13.5% versus 4.6%). Mothers with SLE were less likely to smoke during the first trimester (4.2%) than general population comparators (5.1%). On average, maternal age at delivery and maternal BMI were comparable between mothers with SLE and general population comparators.

Table 1. Baseline characteristics of 1,248 infants born to women with systemic lupus erythematosus (SLE) and 34,886 infants born to general population comparators

	Infants born to mothers with SLE (n =1,248)	**Infants born to general population comparators (n =34,886)**
Female offspring, n (%)	640 (51.3)	16,926 (48.5)
Year of birth, n (%)		
2006-2011	370 (29.7)	15,381 (44.1)
2012-2017	400 (32.0)	10,911 (31.3)
2018-2021	478 (38.4)	8,594 (24.6)
First birth, n (%)	558 (44.7)	14,280 (40.9)
Gestational age, mean ± SD completed weeks	38.7 (2.5)	39.8 (1.8)
Term birth, n (%)	1,080 (86.4)	33,291 (95.4)
Preterm birth, n (%)	168 (13.5)	1,595 (4.6)
32-37 weeks of gestation	136 (10.9)	1,354 (3.9)
<32 weeks of gestation	32 (2.6)	241 (0.7)
Maternal age at delivery, years, mean ± SD	32.3 (4.6)	32.0 (5.0)
Maternal age at delivery in categories, years, n (%)		
<35	882 (70.7)	25,161 (72.1)
≥35	366 (29.3)	9,725 (27.9)
Maternal infection during pregnancy, n (%)	117 (9.4)	1358 (3.9)
Maternal body mass index, mean ± SD *	24.4 (4.3)	24.9 (4.7)
Missing data on body mass index, n (%)	100 (8.0)	2,223 (6.4)
Maternal smoking during first trimester, n (%) *	53 (4.2)	1,763 (5.1)
Missing data on first-trimester smoking, n (%)	71 (5.7)	1,767 (5.1)

SD standard deviation; SLE systematic lupus erythematosus
*Mean or percentage exclude missing values

Risk of infant infections. Twenty-six (2.1%) infants born to mothers with SLE and 414 (1.2%) infants born to mothers without SLE were diagnosed with any infection in the first 72 hours of life (Table 2). Risk of any infection in the first three days was 1.6 times higher than that of infants born to mothers without SLE after adjustment for maternal age at delivery, maternal first-trimester smoking, and calendar year (RR 1.63 [95% CI 1.09-2.42]). Although there were relatively more infants born very preterm with an infection in the first 72 hours to mothers with SLE (11/32, 34.4%) than to mothers without SLE (63/241, 26.1%), the corresponding RR was not significantly higher (1.32 [95%CI 0.77-2.25]). The RR for any infection in the first month of life was lower than the RR for the first three days (1.12 [95%CI 0.88, 1.43)] and results did not differ greatly when stratified by preterm birth (Table 2).

When examining up to one year after birth, the occurrence of any infection was significantly higher in infants born to mothers with SLE (38.3%) than in infants born to mothers without SLE (37.2%), with a corresponding adjusted RR of 1.09 [95% CI 1.01-1.17]. Results among term and preterm births were similar to the overall estimate. The most common first registered infection in the first year of life was upper respiratory (SLE: 13.9% and non-SLE: 12.9%; Supplementary Table 2*)*.

Seventy-three (5.8%) infants born to mothers with SLE and 1,923 (5.5%) infants born to mothers without SLE were hospitalized for infections in the first year of life, and 6 (0.5%) and 162 (0.5%) of those respectively occurred in the first three days. Overall, the number of hospitalized infections was too small stratify by preterm birth. All the results remained similar to the main results in a sensitivity analysis including only first births (Supplementary Table 3).

Table 2. Risk ratios for infection in the first year of life comparing infants born to mothers with systemic lupus erythematosus (SLE) to infants born to mothers from the general population, overall and by preterm birth.

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Any infection in the first three days				
Overall	26/1,248 (2.1)	414/34,886 (1.2)	1.75 (1.19-2.60)	1.63 (1.09-2.42)
Term birth	11/1,083 (1.0)	313/33,291 (0.9)	1.08 (0.60-1.97)	0.98 (0.53-1.80)
Preterm birth (32 to 37 weeks)	4/136 (2.9)	38/1,354 (2.8)	1.05 (0.38-2.89)	1.01 (0.36-2.79)
Very preterm birth (<32 weeks)	11/32 (34.4)	63/241 (26.1)	1.32 (0.78-2.22)	1.32 (0.77-2.25)
Any infection in the first month of life				
Overall	65/1,248 (5.2)	1,586/34,886 (4.5)	1.15 (0.90-1.46)	1.12 (0.88-1.43)
Term birth	44/1,080 (4.1)	1,436/33,291 (4.3)	0.94 (0.70-1.27)	0.92 (0.68-1.23)
Preterm birth (32 to 37 weeks)	10/136 (7.4)	80/1,354 (5.9)	1.24 (0.66-2.34)	1.18 (0.62-2.26)
Very preterm birth (<32 weeks)	11/32 (34.4)	70/241 (29.1)	1.18 (0.71-1.99)	1.19 (0.71-2.02)
Any infection in the first year of life				
Overall	478/1,248 (38.3)	12,985/34,886 (37.2)	1.03 (0.96-1.11)	1.09 (1.01-1.17)
Term birth	400/1,080 (37.0)	12,270/33,291 (36.9)	1.00 (0.93-1.09)	1.07 (0.99-1.16)

Preterm birth (32 to 37 weeks)	59/136 (42.4)	569/1,354 (42.0)	1.03 (0.84-1.26)	1.06 (0.86-1.29)
Very preterm birth (<32 weeks)	19/32 (59.4)	146/241 (60.6)	0.98 (0.72-1.33)	0.99 (0.73-1.35)
Hospitalized infection in the first three days				
Overall	6/1,248 (0.5)	162/34,886 (0.5)	1.04 (0.46-2.33)	0.97 (0.43-2.23)
Term birth	5/1,080 (0.5)	159/33,291 (0.5)	0.97 (0.40-2.36)	0.91 (0.37-2.22)
Preterm birth (32 to 37 weeks)	1/136 (0.7)	3/1,354 (0.2)	NE	NE
Very preterm birth (<32 weeks)	0/32 (0.0)	0/241 (0.0)	NE	NE
Hospitalized infection in the first month of life				
Overall	22/1,248 (1.8)	485/34,886 (1.4)	1.27 (0.83-1.94)	1.25 (0.81-1.91)
Term birth	19/1,080 (1.8)	473/33,291 (1.4)	1.24 (0.79-1.95)	1.21 (0.77-1.92)
Preterm birth (32 to 37 weeks)	3/136 (2.2)	12/1,354 (0.9)	NE	NE
Very preterm birth (<32 weeks)	0/32 (0.0)	0/241 (0.0)	NE	NE
Hospitalized infection in first year of life				
Overall	73/1,248 (5.8)	1,923/34,886 (5.5)	1.06 (0.85-1.33)	1.13 (0.90-1.42)
Term birth	59/1,080 (5.5)	1,776/33,291 (5.3)	1.02 (0.80-1.32)	1.10 (0.85-1.41)

Preterm birth (32 to 37 weeks)	11/136 (8.1)	110/1,354 (8.1)	1.00 (0.55-1.80)	1.03 (0.56-1.88)
Very preterm birth (<32 weeks)	3/32 (9.4)	37/241 (15.4)	0.61 (0.20-1.87)	0.64 (0.20-1.97)

Abbreviation: NE = not estimatable due to low number of events.

Any infection is based on primary and secondary ICD-coded visits in the in- and outpatient components of the National Patient Register (NPR) and prescribed anti-infectives in the Prescribed Drug Register. Hospitalized infections are based on primary ICD-coded visits in the inpatient component of the NPR.

*Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar period (continuous).

The mediating role of preterm birth. Considering all births, 85% of the association between maternal SLE and any infection in the first three days of life was mediated by preterm birth (Table 3). When we examined the first year of life, the proportion mediated through preterm birth was 28%. Looking at first births only, the proportion mediated was 59% for any infection in the first three days and 77% in the first year (Supplementary Table 4*)*. A small proportion of mothers had a visit in inpatient or outpatient care listing an ICD code for infection during pregnancy (9.4% SLE, 3.9% general population), and excluding these pregnancies did not considerably change the estimates in mediation analyses (Supplementary Table 4).

Table 3. Estimates of the mediating effect of preterm birth (<37 weeks gestation) in the association between maternal SLE and infant infections within the first three days and the first year of life. Direct, indirect and total effects are estimated with odds ratios and 95% confidence intervals (OR 95%CI).

Mediator: Preterm birth vs. full term	Direct effect OR 95%CI	Indirect effect through preterm birth OR 95%CI	Total effect OR 95%CI	% Mediated through preterm birth
Outcome				
Any infection in the first 3 days of life	1.10 (0.60-1.61)	1.55 (1.18-1.93)	1.71 (1.00-2.43)	85
Any infection in the first year of life	1.10 (0.97-1.23)	1.03 (0.99-1.07)	1.13 (1.00-1.27)	28

OR odds ratio; CI confidence interval. Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

DISCUSSION

In this Swedish population-based study, we found that infants born to mothers with SLE had a 63% increased risk of any infection in the first three days of life compared with infants born to general population comparators. When looking at the first year of life, we found that the risk of any infection in infants born to mothers with SLE was increased by 9% compared with infants who were not exposed to maternal SLE. Being born preterm could explain 85% of the association between maternal SLE and any infection in the first three days of life, and 28% of the association in the first year of life. We did not find a significant association between maternal SLE and hospitalized infection at any time point in the first year of life.

Information on the risk of infections in infants exposed to maternal SLE during pregnancy is limited. In a previous descriptive study of SLE pregnancies in Sweden using the same data sources but with data only through 2012, the one-year infection risk was significantly higher in infants born to women with SLE compared to infants born to general population comparators.(4) In contrast, we used a broader definition of infections with more ICD-10 codes and anti-infective medications for systemic use and births through 2021. Ignacio and colleagues reported risks of infant infections associated with exposure to maternal SLE, with the risk of any infection in the first 30 days of life of 3.9% in SLE-exposed infants and 2.3% in unexposed infants born to general population comparators.(17) In comparison, we observed a slightly higher risk of infection in both SLE (5.2%) and general population (4.5%) for the same time period.

Women with SLE in our study were three times more likely to deliver preterm than their general population comparators, which has been reported by others.(4, 5, 18) Mediation analysis showed that preterm birth explained a large proportion of the association between infection in the first three days of life and maternal SLE. Maternal infection is a risk factor for preterm delivery, and also for neonatal infection, and the SLE mothers had a higher prevalence of infection during pregnancy compared to the general population.(7) However, when pregnancies with a maternal infection-related hospitalization or outpatient specialst visit were excluded, estimates remained similar to the main analysis. We cannot exclude the possibility that there is residual confounding relating to maternal infection or other unmeasured confounders and therefore these results should be interpreted cautiously. We are most likely not capturing all maternal infections, which is a major cause of preterm birth, by using ICD-

coded visits. Efforts to decrease infant infection should focus on preventing preterm delivery when possible, and consider maternal SLE a risk factor for early neonatal infections, perhaps being extra careful with hospital discharge in the first 72 hours after delivery.

The current study has several strengths. We used a register-based linkage of prospectively collected, population-based data of the entire Swedish population and their infants including the most up-to-date data with follow-up until December 31, 2022. We used a register-based definition of SLE which has good validity.(21) Also, the results of this study can be generalizable to populations with universal access to health care. We realize that our study has also several limitations. We do not have information on breastfeeding, which is associated with a lower risk of respiratory infections with fever, middle ear infection, and infective gastroenteritis in infants.(22) Women with SLE may breastfeed their infants less, especially those born preterm, than general population comparators. While most SLE medications are likely safe in breastfeeding, worries about medication use is an important reason for women with SLE not to breastfeed.(23, 24) Also, there is evidence that infants exposed to maternal SLE born preterm are less likely to be breastfed than babies born at term.(23, 24) Mothers with SLE might seek and/or receive more healthcare than mothers without SLE which would result in more registered infections in the outpatient register of the NPR and more anti-infectives in the Prescribed Drug Register. By using ICD- and ATC-codes to identify infant infections, the exact cause of the infection is not clear as we did not have access to laboratory results and not all infants may have received a laboratory test for type of infection.

The national registers used in this study do not capture information on disease activity, clinical phenotype, severity or duration. Lupus disease activity is an important risk factor for pregnancy complications including preterm delivery.(25) Lupus disease activity and phenotype are strongly related to medication use, and it remains unclear whether medications taken by the mother affect infant infection. However, our results show that the focus should rather be on whether medications affect the risk of *preterm birth*, as it is the main mediator of infant infection.

In conclusion, the risk of any infection in infants born to mothers with SLE is slightly increased during the first year of life. The risk is especially high during the first days

after birth, and most of the risk was driven by preterm birth. The role of maternal infection, immune dysfunction and/or inflammation should be clarified in future studies. Our findings underscore the importance of preventing preterm delivery whenever possible. Preterm delivery may not be avoidable in some circumstances, and therefore to prevent early neonatal infections, maternal SLE could be considered as a risk factor before allowing early discharge from postnatal care. Awareness about the higher infection risk in the first weeks of life, avoiding crowds and people with infections, and vigilance about infection symptoms, should perhaps be recommended to mothers with SLE.

Competing interests

The authors declare no competing interests.

Contributorship

SG, EA and JS designed the study and analysis plan with input from MA and ES. SG and EA conducted the data analysis. SG wrote the first draft of the manuscript and EA, JS, MA and ES provided substantive input to revise and finalise the manuscript.

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Ethical approval

Ethics Review Board in Sweden, decision no. 2021-01148

Data sharing statement

The individual-level data used in this study cannot be publicly made available due to legal restrictions. Please send any requests for the study data to the corresponding author.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of this study.

Key Messages

What is already known about this subject?

Some previous studies report an increased risk of infection in infants born to women with systemic lupus erythematosus (SLE). Previous studies have not accounted for the important role of preterm birth. Preterm birth is more common in SLE pregnancy and a major risk factor for infant infection.

What does this study add?

Infection risk for infants born to women with SLE is especially high the first three days of life and it is mostly driven by preterm birth.

How might this impact on clinical practice?

This study underscores the need to prevent preterm delivery whenever possible. Maternal SLE could be considered as a risk factor for early neonatal infections, and this information could be used to determine how long an infant should stay at the hospital after birth.

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Supplementary Table 1. International classification of disease (ICD) codes used to define infections and anatomical therapeutic chemical (ATC) classification codes used to define treatment for infections in infants.

		ICD-10 (1997-2021)
Upper respiratory	Ear	H60.1-H60.3, H65-H67, H70
	Sinusitis	J01
	Pharyngitis	J02, J39.1, J39.2
	Tonsillitis	J03
	Laryngitis	J04, J05
	Upper respiratory infection, unspecified sites	J06
	Influenza	J09-J11
	Peritonsillar abscess	J36
Lower respiratory	Viral pneumonia	J12
	Pneumonia	J13-J18
	Other, including whooping cough	A37, J20-J22, J85, J86
Gastrointestinal	Intestinal infectious diseases	A00-A09
		K04.0, K04.4, K04.7, K05.0, K05.2, K11.3, K12.2, K35-K37, K61
Other	Erysipelas, lymphadenitis, infections of the skin and subcutaneous tissue	A46, H60.0, L00-L08
	Bacterial infections	A20-A28, A30-A36, A38-A39, A43-A44, A48-A54, A65-A79, B95-B97
	Bacterial sepsis, meningitis and other infections of perinatal period	A40-A41, G00-G01, G03-G04, G06-G09, P36-P39
	Tuberculosis	A15-A19
	Mycoses	A42, B35-B49
	Urinary tract	N13.6, N30.0, N39.0
	Circulatory system	I00, I01, I30.1, I33, I40.0, I41.0, I43.0, I52.0

	Musculoskeletal	M00, M01, M46.2-M46.5M72.6, M86
	Tropical	B50-B83, B85-B94
	Encephalitis, rabies, poliomyelitis, meningitis	A80-A89, G02, G05
	Other viral	A60, A63, A90-A96, A98, A99, B00-B02, B04-B06, B08, B09, B15-B19, B25-B27, B30, B33, B34, B97
	Congenital viral diseases	P35
		ATC codes
Treatment for infection	Anti-infective for systemic use	J01, J02, J04, J05

Supplementary Table 2. Number and type of infections and dispensed prescriptions of antibiotics in the first three months of life in 1,248 infants born to women with systemic lupus erythematosus and 34,886 infants born to general population comparators

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)
Primary and Secondary Outpatient infections, National Patient Register		
Number of infections in the first three days		
0	1,248 (100.0)	34,881 (100.0)
≥1	0 (0.0)	5 (0.0)
Number of infections in the first month		
0	1,228 (98.4)	34,057 (97.6)
≥1	20 (1.6)	829 (2.4)
Number of infections in the first year of life		
0	900 (72.1)	25,926 (74.3)
≥1	348 (27.9)	8,960 (25.7)
Type of first infection in the first year of life		
Upper respiratory	174 (13.9)	4,509 (12.9)
Lower respiratory	45 (3.6)	834 (2.4)
Gastrointestinal	25 (2.0)	786 (2.3)
Other	104 (8.3)	2831 (8.1)
Primary and Secondary Hospitalized infections, National Patient Register		
Number of infections in the first three days		
0	1,225 (98.2)	34,550 (99.0)
≥1	23 (1.8)	336 (1.0)
Number of infections in the first month		
0	1,203 (96.4)	34,190 (98.0)
≥1	45 (3.6)	696 (2.0)
Number of infections in the first year of life		
0	1,145 (91.7)	32,651 (93.6)
≥1	103 (8.3)	2,235 (6.4)
Type of first infection in the first year of life		
Upper respiratory	15 (1.2)	403 (1.0)

Lower respiratory	31 (2.5)	693 (2.0)
Gastrointestinal	7 (0.6)	286 (0.8)
Other	50 (4.0)	853 (1.7)
Only Primary Hospitalized Infections, National Patient Register		
Number of infections in the first three days		
0	1,242 (99.5)	34,724 (99.5)
≥1	6 (0.5)	162 (0.5)
Number of infections in the first month		
0	1,226 (98.2)	34,401 (98.6)
≥1	22 (1.8)	485 (1.4)
Number of infections in the first year of life		
0	1,176 (94.2)	32,998 (94.6)
≥1	72 (5.8)	1,888 (5.4)
Type of first infection in the first year of life		
Upper respiratory	12 (1.0)	342 (1.0)
Lower respiratory	31 (2.5)	686 (2.0)
Gastrointestinal	6 (0.5)	267 (0.8)
Other	23 (1.8)	593 (1.7)
Dispensed prescriptions of anti-infectives, Prescribed Drug Register		
Number of dispensations in the first three days		
0	1,245 (99.8)	34,803 (99.8)
≥1	3 (0.2)	83 (0.2)
Number of dispensations in the first month		
0	1,232 (98.7)	34,447 (98.7)
≥1	16 (1.3)	439 (1.3)
Number of dispensations in the first year of life		
0	1,015 (81.3)	27,868 (79.9)
≥1	233 (18.7)	7,018 (20.1)

Supplementary Table 3. Sensitivity analysis restricted to first births only. Risk ratios for any infection in the first three days and in the first year of life comparing 559 infants born to mothers with SLE to 14,283 infants born to mothers from the general population, overall and by preterm birth

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Any infection in the first three days				
Overall	18/559 (3.2)	211/14,283 (1.5)	2.18 (1.36-3.50)	2.04 (1.26-3.30)
Term birth	8/475 (1.7)	161/13,474 (1.2)	1.41 (0.70-2.85)	1.27 (0.62-2.60)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	16/683 (2.3)	NE	NE
Very preterm birth (<32 weeks)	10/23 (43.5)	34/126 (27.0)	1.61 (0.93-2.79)	1.68 (0.97-2.93)
Any infection in the first month of life				
Overall	26/559 (4.6)	541/14,283 (3.8)	1.23 (0.84-1.80)	1.17 (0.80-1.73)
Term birth	15/475 (3.2)	475/13,474 (3.5)	0.90 (0.54-1.49)	0.85 (0.51-1.42)
Preterm birth (32 to 37 weeks)	1/61 (1.6)	30/683 (4.4)	0.37 (0.05-2.69)	0.36 (0.05-2.57)
Very preterm birth (<32 weeks)	10/23 (43.5)	36/126 (28.6)	1.52 (0.89-2.62)	1.58 (0.91-2.73)
Any infection in the first year of life				

Overall	173/559 (31.0)	4,460/12,283 (31.2)	0.99 (0.87-1.12)	1.06 (0.93-1.20)
Term birth	138/475 (29.1)	4,165/13,474 (30.9)	0.93 (0.81-1.08)	1.01 (0.88-1.17)
Preterm birth (32 to 37 weeks)	19/61 (31.2)	226/683 (33.1)	0.94 (0.64-1.39)	0.96 (0.65-1.41)
Very preterm birth (<32 weeks)	16/23 (69.6)	69/126 (54.8)	1.27 (0.93-1.74)	1.31 (0.95-1.80)
Hospitalized infection in the first three days				
Overall	5/559 (0.9)	89/14,283 (0.6)	1.44 (0.59-3.52)	1.36 (0.55-3.37)
Term birth	5/475 (1.1)	87/13,474 (0.7)	1.63 (0.67-4.00)	1.54 (0.62-3.84)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	2/683 (0.3)	NE	NE
Very preterm birth (<32 weeks)	0/23 (0.0)	0/126 (0.0)	NE	NE
Hospitalized infection in the first month of life				
Overall	8/559 (1.4)	150/14,283 (1.1)	1.36 (0.67-2.76)	1.28 (0.62-2.62)
Term birth	8/475 (1.7)	146/13,474 (1.1)	1.55 (0.77-3.15)	1.44 (0.70-2.96)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	4/683 (0.6)	NE	NE
Very preterm birth (<32 weeks)	0/23 (0.0)	0/126 (0.0)	NE	NE
Hospitalized infection in first year of life				
Overall	25/559 (4.5)	560/14,283 (3.9)	1.14 (0.77-1.69)	1.22 (0.82-1.81)

Term birth	21/475 (4.4)	509/13,474 (3.8)	1.17 (0.76, 1.79)	1.27 (0.83, 1.96)
Preterm birth (32 to 37 weeks)	2/61 (3.3)	38/683 (5.6)	0.59 (0.15-2.38)	0.60 (0.15-2.45)
Very preterm birth (<32 weeks)	2/23 (8.7)	13/126 (10.3)	0.84 (0.20-3.49)	0.98 (0.22-4.44)

Abbreviation: NE = not possible due to low number of events. Any infection is based on primary and secondary ICD-coded visits in the in- and outpatient databases of the National Patient Register and prescribed anti-infectives in the Prescribed Drug Register.
*Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

Supplementary Table 4. Sensitivity analyses restricted to A) first births only and B) mothers without an infection during pregnancy. Estimates of direct effects and effects mediated through preterm birth (<37 weeks gestation) of the association between maternal SLE and infections in infants in the first three days and in the first year of life*

Mediator: Preterm birth (<37 weeks) vs. full term	Direct effect	Indirect effect through preterm birth	Total effect	Mediated through preterm birth, %
A) First births only				
Any infection in the first 3 days of life	1.48 (0.68-2.28)	1.47 (1.06-1.87)	2.1 (1.05-3.29)	59
Any infection in the first year of life	1.02 (0.83-1.22)	1.06 (0.99-1.13)	1.1 (0.88-1.29)	71
B) Mothers without infection during pregnancy				
Any infection in the first 3 days of life	1.16 (0.62, 1.70)	1.61 (1.20, 2.02)	2.87 (1.07, 2.67)	82
Any infection in the first year of life	1.07 (0.94, 1.21)	1.05 (1.00, 1.10)	1.13 (0.99, 1.27)	45

* Values are odd ratios (95% confidence interval) which estimates risk ratios unless indicated otherwise. Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

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Title: The association between maternal systemic lupus erythematosus and infant infection: a population-based cohort study in Sweden

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Running title: Maternal SLE and infant infection risk

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ABSTRACT

Objectives:

To investigate infection risk in offspring born to women with systemic lupus erythematosus (SLE) compared to offspring born to women without SLE, and examine the mediating role of preterm birth.

Methods:

Liveborn singletons born to mothers with SLE (≥2 ICD-coded visits in the National Patient Register (NPR) and MBR, with ≥1 visit before pregnancy) and general population comparators were identified in the Medical Birth Register (MBR; 2006-2021). Infection was defined as any ICD-coded visit in the NPR or anti-infectives in the Prescribed Drug Register. Modified Poisson regression models estimated risk ratios and 95% confidence intervals (RR; 95%CI) of infection associated with maternal SLE adjusted for maternal age, first-trimester smoking, and calendar year. Causal mediation analysis estimated the percentage of the total effect explained by preterm birth.

Results:

Twenty-six of 1,248 (2.1%) SLE offspring and 414 of 34,886 (1.2%) non-SLE offspring had an infection in the first 72 hours (RR 1.62 [95%CI 1.09-2.42]). In the first year of life, risk of infection was higher in SLE offspring than in non-SLE offspring (38.2% vs. 37.2%; RR 1.09 (95%CI 1.01-1.17). The percentage of the total effect of maternal SLE on infant infection mediated through preterm birth was 86% for infection in the first 72 hours and 27% in the first year of life.

Conclusions:

The risk of infection in SLE offspring is most increased in the first three days after birth, with a 62% higher risk of infection compared to non-SLE. A proportion of this association can be explained by preterm birth.

Strengths and limitations of this study

- The use of prospectively collected, contemporary, population-based data from the entire Swedish population minimized selection bias and increased power.
- We were able to link infants to mothers with and without SLE and follow them for one year after birth by using each individual's unique personal identification number.
- Mothers with SLE might seek and/or receive more healthcare than mothers without SLE which would result in an overestimate of the association between maternal SLE and infant infection.
- The national registers used in this study do not capture information on lupus disease activity, clinical phenotype or, severity which might modify the risk of infant infection.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory autoimmune disease that predominantly affects women of childbearing age. Women with SLE have a 20-30% risk of preterm delivery which is two to three times higher than the risk among women without SLE.[1-5] The downstream effect of maternal SLE on infants is not as clear. A previous study from Sweden reported that 21% of infants born to women with SLE had an infection during their first year of life compared to 14% of infants born to mothers without SLE.[4] As the nature of this study was strictly descriptive, it remains unclear if the association between maternal SLE exposure during pregnancy and infections in infants is still present after considering confounding factors and the mediating effect of preterm birth.

Preterm birth (birth before 37 weeks of gestation), is likely an important mediator in the association between maternal SLE and infant infections. Being born preterm is a risk factor for infections, especially early-onset infections of which clinical manifestations usually appear within the first 72 hours.[6, 7] This is partly due to maternal infection (one cause of preterm birth) and immature organs (e.g. lungs and skin). Also, preterm infants often require prolonged intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms, placing them at increased risk for infections. [6, 7] Infants born preterm have on average 1.5 times the total number of infections in the first year of life compared to infants born full-term.[8]

The current study investigates the association between maternal SLE and the risk of infection in infants during the first year of life, and how much of the association can be explained by preterm birth. We used nationwide population-based registers in Sweden to compare infection risk in infants born to women with SLE to infants born to women without SLE.

METHODS

Study setting and sources

In Sweden, access to health care is universal and residents have a unique personal identification number that allows for the linkage of their records in registers. Maternal health during pregnancy, delivery, and neonatal outcomes of over 98% of deliveries in Sweden are registered in the Medical Birth Register (MBR) starting in 1973. Until July 2008, births ≥28 gestational weeks and live births were included. From July 2008, the MBR also included stillbirths ≥22 gestational weeks. Information on sex, year of birth, county of residence, and immigration, from 1968 onward was captured in the Total Population Register (TPR). Date of death is collected in the Cause of Death Register. Hospitalization data with national coverage from 1987 onward and non-primary care specialized outpatient visits since 2001 are captured in the National Patient Register (NPR). Primary and secondary diagnoses are listed for each visit using International Classification of Diseases (ICD) codes. Since July 2005, dispensed prescriptions of medications in the Swedish population are captured in the Prescribed Drug Register (PDR) using Anatomical Therapeutic Chemical (ATC) codes.

Study population

Infants born to mothers with SLE (exposed) and without SLE from the general population (unexposed) were identified by linking the NPR to the MBR. Women with ≥1 ICD-coded visits for SLE (ICD-10: M32, excluding M32.0 drug-induced lupus) in the inpatient or outpatient records of the NPR were matched to ten randomly sampled comparators from the general population without SLE, identified in the TPR, on year of birth, sex, calendar time, and residential location. We further restricted the women with SLE to have ≥2 visits listing SLE, at least one of which was required to be given at a department or specialist that diagnoses, treats or manages SLE (rheumatology, dermatology, nephrology, internal medicine and/or paediatrics). This definition is estimated to have a positive predictive value of 80% in women,[9] but its accuracy has not been evaluated for identifying pregnant women with prevalent SLE.

From this population of women with SLE and the general population comparators without SLE, we identified those who gave birth to a liveborn singleton registered in the MBR between March 2006 (as the PDR started in July 2005) and December 2021

without missing data on gestational age. A flow chart of the study population selection is depicted in Figure 1.

Maternal SLE at delivery

The infants were considered to be born to a mother with SLE if the mother had at least one SLE discharge code before pregnancy at a specialist clinic (rheumatology, dermatology, nephrology, internal medicine and/or paediatrics). The first observed SLE discharge code was used as a proxy for diagnosis date as it is the first observed diagnosis in our data, which does not include primary care. However, SLE diagnosis typically is given by specialists, therefore this is a reasonable proxy. Infants born to women with only one visit for SLE before delivery or with no visits with a specialist before pregnancy were excluded to minimise misclassification of maternal SLE. There were no general population comparators with an SLE discharge code before pregnancy.

The study period was from the infant's date of birth for one year, death, or emigration, whichever came first. Ethical approval was granted by the Ethics Review Authority in Sweden (DNR 2021-01148).

Infections in infants

Any infant infection was identified using both primary and secondary ICD-coded visits in the inpatient and outpatient records of the NPR and dispensed prescriptions of anti-infectives in the PDR (the majority of which were antibiotics). We also examined hospitalized infections separately, defined as a hospitalization listing infection as the primary diagnosis in the inpatient records of the NPR. The first infection during follow-up was categorized into upper respiratory, lower respiratory, gastrointestinal, and other infections. For a list of ICD codes for infections and ATC codes for dispensed prescriptions of anti-infectives, see Supplementary Table 1, adapted from Sørup et al. (2016), Miller et al. (2016) and Bröms et al. (2020).[10-12] For any infection and hospitalized infection, we identified those occurring in the first three days (early-onset), within one month and within one year of birth. We examined infections in the first three days because it has a different pathogenesis than infections later in life and is associated with serious complications that can be life-threatening.

Preterm birth and other covariates

Preterm birth (birth before 37 weeks of gestation) and very preterm birth (birth before 32 weeks of gestation) were identified in the MBR. Additional data from the MBR included the infant's sex, infant's date of birth, parity (first or subsequent birth), gestational age in weeks, maternal age at delivery, and self-reported maternal first trimester smoking (yes/no/missing). Maternal height and weight collected at the first prenatal visit was used to calculate the body mass index (BMI) as weight divided by height squared (kg/m^2). Maternal infection during pregnancy was collected from the NPR and defined as an inpatient or outpatient visit listing an ICD code for infection.

Statistical analysis

Continuous variables were described using means and standard deviations (SD) and categorical variables were described with frequencies and column percentages. We calculated risk ratios (RR) and corresponding 95% confidence intervals using modified Poisson regression models to estimate the risk of infant infection comparing infants born to mothers with SLE to infants born to general population comparators.[13] Models were adjusted for maternal age at delivery (continuous), maternal fist-trimester smoking (yes/no/missing), and calendar year (continuous). RRs for any infant infection in three time windows were estimated: 1) within the first 72 hours, 2) the first month and 3) the first year of life, overall and by preterm birth. RRs were also estimated for hospitalized infection in the three time windows. In a sensitivity analysis, we reran all models among only first births. It has been shown that outcomes from the first pregnancy might be less favorable than subsequent pregnancies.[14]

We conducted a mediation analysis using a casual inference counterfactual approach to examine how much of the association between maternal SLE and any infection in infants could be explained by preterm birth.[15] Mediation analysis can be used to assess factors that are caused by the exposure (maternal SLE) and cause the outcome (infant infection) to better understand the relationship between exposure and outcome and to ultimately identify factors which can be intervened upon. Causal mediation analysis accommodates interaction between the exposure and mediator. We investigated the how much of the association between maternal SLE and infant infection operates through the mediating effect of preterm birth. Total effects were separated into natural direct effects and natural indirect effects through preterm birth. Results were reported on the odds ratio scale which estimates the RR and is

comparable with the RR. Based on knowledge from the literature, causal mediation models were adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous) to account for exposure-mediator, mediator-outcome, and exposure-outcome confounding.[16] We included an interaction between maternal SLE and preterm birth in the model. Because maternal infection is associated with both preterm birth and infant infection, we also performed a sensitivity analysis excluding mothers with an infection during pregnancy in a sensitivity analysis. All data management and analyses were performed using SAS, version 9.4.

RESULTS

Baseline characteristics of mothers and infants. We included 1,248 infants born to mothers with SLE and 34,886 infants born to general population comparators (Table 1). The proportion of births that were first born was higher among SLE-exposed infants compared to those infants born to mothers without SLE (44.7% versus 40.9%), and SLE-exposed infants were almost three times more likely to be born preterm (13.5% versus 4.6%). Mothers with SLE were less likely to smoke during the first trimester (4.2%) than general population comparators (5.1%). On average, maternal age at delivery and maternal BMI were comparable between mothers with SLE and general population comparators.

Table 1. Baseline characteristics of 1,248 infants born to women with systemic lupus erythematosus (SLE) and 34,886 infants born to general population comparators

	Infants born to mothers with SLE (n =1,248)	**Infants born to general population comparators (n =34,886)**
Female offspring, n (%)	640 (51.3)	16,926 (48.5)
Year of birth, n (%)		
2006-2011	370 (29.7)	15,381 (44.1)
2012-2017	400 (32.0)	10,911 (31.3)
2018-2021	478 (38.4)	8,594 (24.6)
First birth, n (%)	558 (44.7)	14,280 (40.9)
Gestational age, mean ± SD completed weeks	38.7 (2.5)	39.8 (1.8)
Term birth, n (%)	1,080 (86.4)	33,291 (95.4)
Preterm birth, n (%)	168 (13.5)	1,595 (4.6)
32-37 weeks of gestation	136 (10.9)	1,354 (3.9)
<32 weeks of gestation	32 (2.6)	241 (0.7)
Maternal age at delivery, years, mean ± SD	32.3 (4.6)	32.0 (5.0)
Maternal age at delivery in categories, years, n (%)		
<35	882 (70.7)	25,161 (72.1)
≥35	366 (29.3)	9,725 (27.9)
Maternal infection during pregnancy, n (%)	117 (9.4)	1358 (3.9)
Maternal body mass index, mean ± SD *	24.4 (4.3)	24.9 (4.7)
Missing data on body mass index, n (%)	100 (8.0)	2,223 (6.4)
Maternal smoking during first trimester, n (%) *	53 (4.2)	1,763 (5.1)
Missing data on first-trimester smoking, n (%)	71 (5.7)	1,767 (5.1)

SD standard deviation; SLE systematic lupus erythematosus
*Mean or percentage exclude missing values

Risk of infant infections. Twenty-six (2.1%) infants born to mothers with SLE and 414 (1.2%) infants born to mothers without SLE were diagnosed with any infection in the first 72 hours of life (Table 2). The most common first registered infection in the first year of life was upper respiratory (SLE: 13.9% and non-SLE: 12.9%; Supplementary Table 2).

Relative risk of infection in the first 72 hours associated with maternal SLE was 1.6 compared to infants born to mothers without SLE (adjusted RR 1.63 [95% CI 1.09-2.42]). The RR for any infection in the first month of life was 1.12 [95%CI 0.88, 1.43] and results did not differ greatly when stratified by preterm birth (Table 2). When examining up to one year after birth, the occurrence of any infection was significantly higher in infants born to mothers with SLE (38.3%) than in infants born to mothers without SLE (37.2%), with a corresponding adjusted RR of 1.09 [95% CI 1.01-1.17].

In the first 72 hours, there was a higher percentage of infants born very preterm with an infection to mothers with SLE (11/32, 34.4%) than to mothers without SLE (63/241, 26.1%), although the corresponding RR was not significantly higher (1.32 [95%CI 0.77-2.25]). Results among term and preterm births were similar to the overall estimates for the other time windows.

Seventy-three (5.8%) infants born to mothers with SLE and 1,923 (5.5%) infants born to mothers without SLE were hospitalized for infections in the first year of life, and 6 (0.5%) and 162 (0.5%) of those respectively occurred in the first three days. Overall, the number of hospitalized infections was too small to stratify by preterm birth.

All the results remained similar to the main results in a sensitivity analysis including only first births, although with limited power for some subgroups (Supplementary Table 3).

Table 2. Risk ratios for infection in the first year of life comparing infants born to mothers with systemic lupus erythematosus (SLE) to infants born to mothers from the general population, overall and by preterm birth.

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Any infection in the first three days				
Overall	26/1,248 (2.1)	414/34,886 (1.2)	1.75 (1.19-2.60)	1.63 (1.09-2.42)
Term birth	11/1,083 (1.0)	313/33,291 (0.9)	1.08 (0.60-1.97)	0.98 (0.53-1.80)
Preterm birth (32 to 37 weeks)	4/136 (2.9)	38/1,354 (2.8)	1.05 (0.38-2.89)	1.01 (0.36-2.79)
Very preterm birth (<32 weeks)	11/32 (34.4)	63/241 (26.1)	1.32 (0.78-2.22)	1.32 (0.77-2.25)
Any infection in the first month of life				
Overall	65/1,248 (5.2)	1,586/34,886 (4.5)	1.15 (0.90-1.46)	1.12 (0.88-1.43)
Term birth	44/1,080 (4.1)	1,436/33,291 (4.3)	0.94 (0.70-1.27)	0.92 (0.68-1.23)
Preterm birth (32 to 37 weeks)	10/136 (7.4)	80/1,354 (5.9)	1.24 (0.66-2.34)	1.18 (0.62-2.26)
Very preterm birth (<32 weeks)	11/32 (34.4)	70/241 (29.1)	1.18 (0.71-1.99)	1.19 (0.71-2.02)
Any infection in the first year of life				
Overall	478/1,248 (38.3)	12,985/34,886 (37.2)	1.03 (0.96-1.11)	1.09 (1.01-1.17)
Term birth	400/1,080 (37.0)	12,270/33,291 (36.9)	1.00 (0.93-1.09)	1.07 (0.99-1.16)

Preterm birth (32 to 37 weeks)	59/136 (42.4)	569/1,354 (42.0)	1.03 (0.84-1.26)	1.06 (0.86-1.29)
Very preterm birth (<32 weeks)	19/32 (59.4)	146/241 (60.6)	0.98 (0.72-1.33)	0.99 (0.73-1.35)
Hospitalized infection in the first three days				
Overall	6/1,248 (0.5)	162/34,886 (0.5)	1.04 (0.46-2.33)	0.97 (0.43-2.23)
Term birth	5/1,080 (0.5)	159/33,291 (0.5)	0.97 (0.40-2.36)	0.91 (0.37-2.22)
Preterm birth (32 to 37 weeks)	1/136 (0.7)	3/1,354 (0.2)	NE	NE
Very preterm birth (<32 weeks)	0/32 (0.0)	0/241 (0.0)	NE	NE
Hospitalized infection in the first month of life				
Overall	22/1,248 (1.8)	485/34,886 (1.4)	1.27 (0.83-1.94)	1.25 (0.81-1.91)
Term birth	19/1,080 (1.8)	473/33,291 (1.4)	1.24 (0.79-1.95)	1.21 (0.77-1.92)
Preterm birth (32 to 37 weeks)	3/136 (2.2)	12/1,354 (0.9)	NE	NE
Very preterm birth (<32 weeks)	0/32 (0.0)	0/241 (0.0)	NE	NE
Hospitalized infection in first year of life				
Overall	73/1,248 (5.8)	1,923/34,886 (5.5)	1.06 (0.85-1.33)	1.13 (0.90-1.42)
Term birth	59/1,080 (5.5)	1,776/33,291 (5.3)	1.02 (0.80-1.32)	1.10 (0.85-1.41)

Preterm birth (32 to 37 weeks)	11/136 (8.1)	110/1,354 (8.1)	1.00 (0.55-1.80)	1.03 (0.56-1.88)
Very preterm birth (<32 weeks)	3/32 (9.4)	37/241 (15.4)	0.61 (0.20-1.87)	0.64 (0.20-1.97)

Abbreviation: NE = not estimatable due to low number of events.

Any infection is based on primary and secondary ICD-coded visits in the in- and outpatient components of the National Patient Register (NPR) and prescribed anti-infectives in the Prescribed Drug Register. Hospitalized infections are based on primary ICD-coded visits in the inpatient component of the NPR.

*Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar period (continuous).

The mediating role of preterm birth. Considering all births, 85% (95%CI 27-144) of the association between maternal SLE and any infection in the first three days of life was mediated by preterm birth (Table 3). The proportion mediated through preterm birth for the first year of life was 28% (95%CI -10-66). Looking at first births only, the proportion mediated was 59% (95%CI 19-98) for any infection in the first three days and 77% (95%CI -117-272) in the first year (Supplementary Table 4). A small proportion of mothers had a visit in inpatient or outpatient care listing an ICD code for infection during pregnancy (9.4% SLE, 3.9% general population), and excluding these pregnancies did not considerably change the estimates in mediation analyses (Supplementary Table 4).

Table 3. Estimates of the mediating effect of preterm birth (<37 weeks gestation) in the association between maternal SLE and infant infections within the first three days and the first year of life. Direct, indirect and total effects are estimated with odds ratios and 95% confidence intervals (OR 95%CI).

Mediator: Preterm birth vs. full term	Direct effect OR (95%CI)	Indirect effect through preterm birth OR (95%CI)	Total effect OR 95%CI	% Mediated through preterm birth (95% CI)
Outcome				
Any infection in the first 3 days of life	1.10 (0.60-1.61)	1.55 (1.18-1.93)	(1.00-2.43)	85 (27-144)
Any infection in the first year of life	1.10 (0.97-1.23)	1.03 (0.99-1.07)	.13 (1.00-1.27)	28 (-10 - 66)

OR odds ratio; CI confidence interval. Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

DISCUSSION

In this population-based study in Sweden, infants born to mothers with SLE had a 63% increased risk of any infection in the first three days of life compared with infants born to general population comparators. In the first year of life, the risk of any infection in infants born to mothers with SLE was 9% higher than infants who were not exposed to maternal SLE. Being born preterm accounted for a proportion of the association between maternal SLE and any infection in the first three days of life. We did not find a significant association between maternal SLE and hospitalized infection at any time point in the first year of life.

Information on the risk of infections in infants exposed to maternal SLE during pregnancy is limited. In a previous descriptive study of SLE pregnancies in Sweden using the same data sources but with data only through 2012, the one-year infection risk was significantly higher in infants born to women with SLE compared to infants born to general population comparators.[4] In contrast, we used a broader definition of infections with more ICD-10 codes and anti-infective medications for systemic use and births through 2021. Ignacio and colleagues reported risks of infant infections associated with exposure to maternal SLE, with the risk of any infection in the first 30 days of life of 3.9% in SLE-exposed infants and 2.3% in unexposed infants born to general population comparators.[17] In comparison, we observed a slightly higher risk of infection in both SLE (5.2%) and general population (4.5%) for the same time period.

Women with SLE in our study were three times more likely to deliver preterm than their general population comparators, which has been reported by others.[4, 5, 18] Mediation analysis showed that preterm birth explained a proportion of the association between infection in the first three days of life and maternal SLE. Maternal infection is a risk factor for preterm birth, and also for neonatal infection, and the SLE mothers had a higher prevalence of infection during pregnancy compared to the general population.(7) However, when pregnancies with a maternal infection-related hospitalization or outpatient specialst visit were excluded, estimates remained similar to the main analysis. We cannot exclude the possibility that there is residual confounding related to maternal infection or other unmeasured confounders and therefore these results should be interpreted cautiously. We are most likely not capturing all maternal infections by using ICD-coded visits. Efforts to decrease infant infection should focus on preventing preterm delivery when possible. Maternal SLE

should be considered a risk factor for early neonatal infections and could be used to assess risk when considering early hospital discharge.

The current study has several strengths. We used a register-based linkage of prospectively collected, population-based data of the entire Swedish population and their infants including the most up-to-date data with follow-up until December 31, 2022. We used a register-based definition of SLE which has good validity.[19] Also, the results of this study can be generalizable to populations with universal access to health care.

We realize that our study has also several limitations. We do not have information on breastfeeding, which is associated with a lower risk of respiratory infections with fever, middle ear infection, and infective gastroenteritis in infants.[20] Women with SLE may breastfeed their infants less, especially those born preterm, than general population comparators. While most SLE medications are likely safe in breastfeeding, worries about medication use is an important reason for women with SLE not to breastfeed.[21, 22] Also, there is evidence that infants exposed to maternal SLE born preterm are less likely to be breastfed than babies born at term.[21, 22] Mothers with SLE might seek and/or receive more healthcare than mothers without SLE which would result in more registered outpatient infections and more prescriptions of anti-infectives. By using ICD- and ATC-codes to identify infant infections, the exact cause of the infection is not clear as we did not have access to laboratory results and not all infants may have received a laboratory test for type of infection. The national registers do not capture information on disease activity, clinical phenotype or severity and thus were not accounted for in this study. Lupus disease activity is an important risk factor for pregnancy complications including preterm delivery.[23] Lupus disease activity and phenotype are strongly related to medication use, and all of these factors could affect infant infection. We do not have information on rituximab use during pregnancy, which depletes B cells in the mother and baby and affects infant infection risk. However, during the study's time period rituximab was not recommended for use during pregnancy, except in extremely rare cases, according to treatment guidelines by the Swedish Society of Rheumatology. Therefore we do not believe that rituximab has greatly affected our results. Future studies should investigate the relationship between SLE-related characteristics and infant infection with more clinically detailed data, with a focus on preterm infants who carry the majority of the risk. Some analyses were

limited in power, resulting in wide confidence intervals and the proportion mediated estimates are unstable when sample sizes are small.[24] Although we adjusted for several confounders of the exposure-mediator and mediator-outcome relationships, there is likely to be residual confounding.

In conclusion, the risk of infection in infants born to mothers with SLE is slightly increased during the first year of life. The relative risk is highest during the first days after birth, and some of the increased risk was accounted for by preterm birth. The role of maternal infection, immune dysfunction and/or inflammation should be clarified in future studies. Our findings underscore the importance of preventing preterm delivery whenever possible, but preterm delivery may not be avoidable in some circumstances and it is sometimes necessary for the health of the mother and infant. Therefore, to prevent early neonatal infections, maternal SLE could be considered as a risk factor before allowing early discharge from postnatal care. Awareness about the higher infection risk in the first weeks of life, avoiding crowds and people with infections, and vigilance about infection symptoms, should perhaps be recommended to mothers with SLE.

Competing interests

The authors declare no competing interests.

Contributorship

EA is responsible for the overall content as guarantor. SG, EA and JS designed the study and analysis plan with input from MA and ES. SG and EA conducted the data analysis. SG wrote the first draft of the manuscript and EA, JS, MA and ES provided substantive input to revise and finalise the manuscript.

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Ethical approval

Ethics Review Board in Sweden, decision no. 2021-01148

Data sharing statement

The individual-level data used in this study cannot be publicly made available due to legal restrictions. Please send any requests for the study data to the corresponding author.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of this study.

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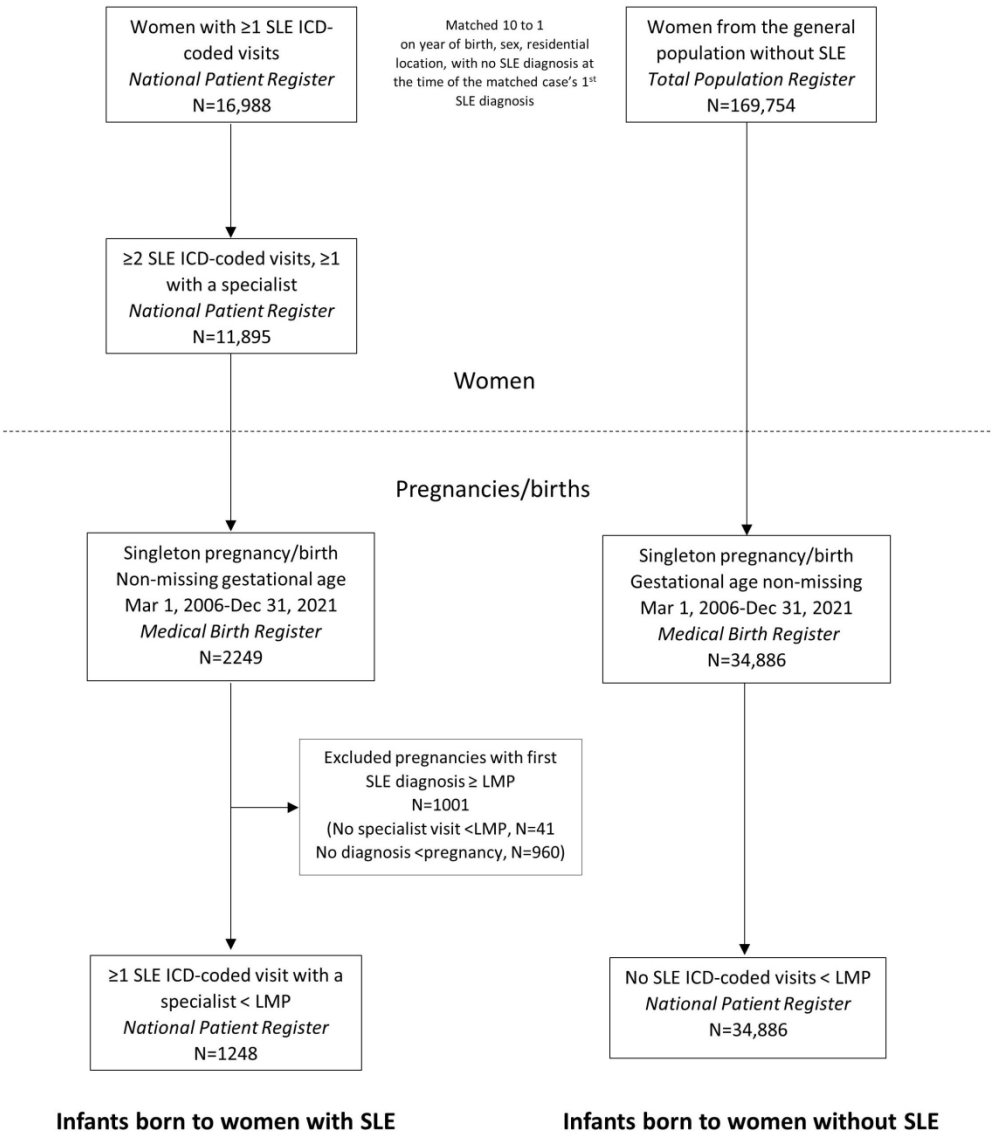
Figure Legend

Figure 1. Flow chart of study population selection.



Flow chart of study population selection

190x229mm (300 x 300 DPI)

Supplementary Table 1. International classification of disease (ICD) codes used to define infections and anatomical therapeutic chemical (ATC) classification codes used to define treatment for infections in infants.

		ICD-10 (1997-2021)
Upper respiratory	Ear	H60.1-H60.3, H65-H67, H70
	Sinusitis	J01
	Pharyngitis	J02, J39.1, J39.2
	Tonsillitis	J03
	Laryngitis	J04, J05
	Upper respiratory infection, unspecified sites	J06
	Influenza	J09-J11
	Peritonsillar abscess	J36
Lower respiratory	Viral pneumonia	J12
	Pneumonia	J13-J18
	Other, including whooping cough	A37, J20-J22, J85, J86
Gastrointestinal	Intestinal infectious diseases	A00-A09
		K04.0, K04.4, K04.7, K05.0, K05.2, K11.3, K12.2, K35-K37, K61
Other	Erysipelas, lymphadenitis, infections of the skin and subcutaneous tissue	A46, H60.0, L00-L08
	Bacterial infections	A20-A28, A30-A36, A38-A39, A43-A44, A48-A54, A65-A79, B95-B97
	Bacterial sepsis, meningitis and other infections of perinatal period	A40-A41, G00-G01, G03-G04, G06-G09, P36-P39
	Tuberculosis	A15-A19
	Mycoses	A42, B35-B49
	Urinary tract	N13.6, N30.0, N39.0
	Circulatory system	I00, I01, I30.1, I33, I40.0, I41.0, I43.0, I52.0

	Musculoskeletal	M00, M01, M46.2-M46.5M72.6, M86
	Tropical	B50-B83, B85-B94
	Encephalitis, rabies, poliomyelitis, meningitis	A80-A89, G02, G05
	Other viral	A60, A63, A90-A96, A98, A99, B00-B02, B04-B06, B08, B09, B15-B19, B25-B27, B30, B33, B34, B97
	Congenital viral diseases	P35
		ATC codes
Treatment for infection	Anti-infective for systemic use	J01, J02, J04, J05

Supplementary Table 2. Number and type of infections and dispensed prescriptions of antibiotics in the first three months of life in 1,248 infants born to women with systemic lupus erythematosus and 34,886 infants born to general population comparators

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)
Primary and Secondary Outpatient infections, National Patient Register		
Number of infections in the first three days		
0	1,248 (100.0)	34,881 (100.0)
≥1	0 (0.0)	5 (0.0)
Number of infections in the first month		
0	1,228 (98.4)	34,057 (97.6)
≥1	20 (1.6)	829 (2.4)
Number of infections in the first year of life		
0	900 (72.1)	25,926 (74.3)
≥1	348 (27.9)	8,960 (25.7)
Type of first infection in the first year of life		
Upper respiratory	174 (13.9)	4,509 (12.9)
Lower respiratory	45 (3.6)	834 (2.4)
Gastrointestinal	25 (2.0)	786 (2.3)
Other	104 (8.3)	2831 (8.1)
Primary and Secondary Hospitalized infections, National Patient Register		
Number of infections in the first three days		
0	1,225 (98.2)	34,550 (99.0)
≥1	23 (1.8)	336 (1.0)
Number of infections in the first month		
0	1,203 (96.4)	34,190 (98.0)
≥1	45 (3.6)	696 (2.0)
Number of infections in the first year of life		
0	1,145 (91.7)	32,651 (93.6)
≥1	103 (8.3)	2,235 (6.4)
Type of first infection in the first year of life		
Upper respiratory	15 (1.2)	403 (1.0)

Lower respiratory	31 (2.5)	693 (2.0)
Gastrointestinal	7 (0.6)	286 (0.8)
Other	50 (4.0)	853 (1.7)
Only Primary Hospitalized Infections, National Patient Register		
Number of infections in the first three days		
0	1,242 (99.5)	34,724 (99.5)
≥1	6 (0.5)	162 (0.5)
Number of infections in the first month		
0	1,226 (98.2)	34,401 (98.6)
≥1	22 (1.8)	485 (1.4)
Number of infections in the first year of life		
0	1,176 (94.2)	32,998 (94.6)
≥1	72 (5.8)	1,888 (5.4)
Type of first infection in the first year of life		
Upper respiratory	12 (1.0)	342 (1.0)
Lower respiratory	31 (2.5)	686 (2.0)
Gastrointestinal	6 (0.5)	267 (0.8)
Other	23 (1.8)	593 (1.7)
Dispensed prescriptions of anti-infectives, Prescribed Drug Register		
Number of dispensations in the first three days		
0	1,245 (99.8)	34,803 (99.8)
≥1	3 (0.2)	83 (0.2)
Number of dispensations in the first month		
0	1,232 (98.7)	34,447 (98.7)
≥1	16 (1.3)	439 (1.3)
Number of dispensations in the first year of life		
0	1,015 (81.3)	27,868 (79.9)
≥1	233 (18.7)	7,018 (20.1)

Supplementary Table 3. Sensitivity analysis restricted to first births only. Risk ratios for any infection in the first three days and in the first year of life comparing 559 infants born to mothers with SLE to 14,283 infants born to mothers from the general population, overall and by preterm birth

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Any infection in the first three days				
Overall	18/559 (3.2)	211/14,283 (1.5)	2.18 (1.36-3.50)	2.04 (1.26-3.30)
Term birth	8/475 (1.7)	161/13,474 (1.2)	1.41 (0.70-2.85)	1.27 (0.62-2.60)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	16/683 (2.3)	NE	NE
Very preterm birth (<32 weeks)	10/23 (43.5)	34/126 (27.0)	1.61 (0.93-2.79)	1.68 (0.97-2.93)
Any infection in the first month of life				
Overall	26/559 (4.6)	541/14,283 (3.8)	1.23 (0.84-1.80)	1.17 (0.80-1.73)
Term birth	15/475 (3.2)	475/13,474 (3.5)	0.90 (0.54-1.49)	0.85 (0.51-1.42)
Preterm birth (32 to 37 weeks)	1/61 (1.6)	30/683 (4.4)	0.37 (0.05-2.69)	0.36 (0.05-2.57)
Very preterm birth (<32 weeks)	10/23 (43.5)	36/126 (28.6)	1.52 (0.89-2.62)	1.58 (0.91-2.73)
Any infection in the first year of life				

Overall	173/559 (31.0)	4,460/12,283 (31.2)	0.99 (0.87-1.12)	1.06 (0.93-1.20)
Term birth	138/475 (29.1)	4,165/13,474 (30.9)	0.93 (0.81-1.08)	1.01 (0.88-1.17)
Preterm birth (32 to 37 weeks)	19/61 (31.2)	226/683 (33.1)	0.94 (0.64-1.39)	0.96 (0.65-1.41)
Very preterm birth (<32 weeks)	16/23 (69.6)	69/126 (54.8)	1.27 (0.93-1.74)	1.31 (0.95-1.80)
Hospitalized infection in the first three days				
Overall	5/559 (0.9)	89/14,283 (0.6)	1.44 (0.59-3.52)	1.36 (0.55-3.37)
Term birth	5/475 (1.1)	87/13,474 (0.7)	1.63 (0.67-4.00)	1.54 (0.62-3.84)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	2/683 (0.3)	NE	NE
Very preterm birth (<32 weeks)	0/23 (0.0)	0/126 (0.0)	NE	NE
Hospitalized infection in the first month of life				
Overall	8/559 (1.4)	150/14,283 (1.1)	1.36 (0.67-2.76)	1.28 (0.62-2.62)
Term birth	8/475 (1.7)	146/13,474 (1.1)	1.55 (0.77-3.15)	1.44 (0.70-2.96)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	4/683 (0.6)	NE	NE
Very preterm birth (<32 weeks)	0/23 (0.0)	0/126 (0.0)	NE	NE
Hospitalized infection in first year of life				
Overall	25/559 (4.5)	560/14,283 (3.9)	1.14 (0.77-1.69)	1.22 (0.82-1.81)

Term birth	21/475 (4.4)	509/13,474 (3.8)	1.17 (0.76, 1.79)	1.27 (0.83, 1.96)
Preterm birth (32 to 37 weeks)	2/61 (3.3)	38/683 (5.6)	0.59 (0.15-2.38)	0.60 (0.15-2.45)
Very preterm birth (<32 weeks)	2/23 (8.7)	13/126 (10.3)	0.84 (0.20-3.49)	0.98 (0.22-4.44)

Abbreviation: NE = not possible due to low number of events. Any infection is based on primary and secondary ICD-coded visits in the in- and outpatient databases of the National Patient Register and prescribed anti-infectives in the Prescribed Drug Register.
*Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

Supplementary Table 4. Sensitivity analyses restricted to A) first births only and B) mothers without an infection during pregnancy. Estimates of direct effects and effects mediated through preterm birth (<37 weeks gestation) of the association between maternal SLE and infections in infants in the first three days and in the first year of life*

Mediator: Preterm birth (<37 weeks) vs. full term	Direct effect	Indirect effect through preterm birth	Total effect	Mediated through preterm birth, % (95% CI)
A) First births only				
Any infection in the first 3 days of life	1.48 (0.68-2.28)	1.47 (1.06-1.87)	2.18 (1.05-3.29)	59 (19-98)
Any infection in the first year of life	1.02 (0.83-1.22)	1.06 (0.99-1.13)	1.08 (0.88-1.29)	77 (1-117 – 272)
B) Mothers without infection during pregnancy				
Any infection in the first 3 days of life	1.16 (0.62, 1.70)	1.61 (1.20, 2.02)	1.87 (1.07, 2.67)	82 (33-130)
Any infection in the first year of life	1.07 (0.94, 1.21)	1.05 (1.00, 1.10)	1.13 (0.99, 1.27)	45 (-8-98)

* Values are odd ratios (95% confidence interval) which estimates risk ratios unless indicated otherwise. Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

Supplementary Table 1. International classification of disease (ICD) codes used to define infections and anatomical therapeutic chemical (ATC) classification codes used to define treatment for infections in infants.

		ICD-10 (1997-2021)
Upper respiratory	Ear	H60.1-H60.3, H65-H67, H70
	Sinusitis	J01
	Pharyngitis	J02, J39.1, J39.2
	Tonsillitis	J03
	Laryngitis	J04, J05
	Upper respiratory infection, unspecified sites	J06
	Influenza	J09-J11
	Peritonsillar abscess	J36
Lower respiratory	Viral pneumonia	J12
	Pneumonia	J13-J18
	Other, including whooping cough	A37, J20-J22, J85, J86
Gastrointestinal	Intestinal infectious diseases	A00-A09
		K04.0, K04.4, K04.7, K05.0, K05.2, K11.3, K12.2, K35-K37, K61
Other	Erysipelas, lymphadenitis, infections of the skin and subcutaneous tissue	A46, H60.0, L00-L08
	Bacterial infections	A20-A28, A30-A36, A38-A39, A43-A44, A48-A54, A65-A79, B95-B97
	Bacterial sepsis, meningitis and other infections of perinatal period	A40-A41, G00-G01, G03-G04, G06-G09, P36-P39
	Tuberculosis	A15-A19
	Mycoses	A42, B35-B49
	Urinary tract	N13.6, N30.0, N39.0
	Circulatory system	I00, I01, I30.1, I33, I40.0, I41.0, I43.0, I52.0

	Musculoskeletal	M00, M01, M46.2-M46.5M72.6, M86
	Tropical	B50-B83, B85-B94
	Encephalitis, rabies, poliomyelitis, meningitis	A80-A89, G02, G05
	Other viral	A60, A63, A90-A96, A98, A99, B00-B02, B04-B06, B08, B09, B15-B19, B25-B27, B30, B33, B34, B97
	Congenital viral diseases	P35
		ATC codes
Treatment for infection	Anti-infective for systemic use	J01, J02, J04, J05

Supplementary Table 2. Number and type of infections and dispensed prescriptions of antibiotics in the first three months of life in 1,248 infants born to women with systemic lupus erythematosus and 34,886 infants born to general population comparators

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)
Primary and Secondary Outpatient infections, National Patient Register		
Number of infections in the first three days		
0	1,248 (100.0)	34,881 (100.0)
≥1	0 (0.0)	5 (0.0)
Number of infections in the first month		
0	1,228 (98.4)	34,057 (97.6)
≥1	20 (1.6)	829 (2.4)
Number of infections in the first year of life		
0	900 (72.1)	25,926 (74.3)
≥1	348 (27.9)	8,960 (25.7)
Type of first infection in the first year of life		
Upper respiratory	174 (13.9)	4,509 (12.9)
Lower respiratory	45 (3.6)	834 (2.4)
Gastrointestinal	25 (2.0)	786 (2.3)
Other	104 (8.3)	2831 (8.1)
Primary and Secondary Hospitalized infections, National Patient Register		
Number of infections in the first three days		
0	1,225 (98.2)	34,550 (99.0)
≥1	23 (1.8)	336 (1.0)
Number of infections in the first month		
0	1,203 (96.4)	34,190 (98.0)
≥1	45 (3.6)	696 (2.0)
Number of infections in the first year of life		
0	1,145 (91.7)	32,651 (93.6)
≥1	103 (8.3)	2,235 (6.4)
Type of first infection in the first year of life		
Upper respiratory	15 (1.2)	403 (1.0)

Lower respiratory	31 (2.5)	693 (2.0)
Gastrointestinal	7 (0.6)	286 (0.8)
Other	50 (4.0)	853 (1.7)
Only Primary Hospitalized Infections, National Patient Register		
Number of infections in the first three days		
0	1,242 (99.5)	34,724 (99.5)
≥1	6 (0.5)	162 (0.5)
Number of infections in the first month		
0	1,226 (98.2)	34,401 (98.6)
≥1	22 (1.8)	485 (1.4)
Number of infections in the first year of life		
0	1,176 (94.2)	32,998 (94.6)
≥1	72 (5.8)	1,888 (5.4)
Type of first infection in the first year of life		
Upper respiratory	12 (1.0)	342 (1.0)
Lower respiratory	31 (2.5)	686 (2.0)
Gastrointestinal	6 (0.5)	267 (0.8)
Other	23 (1.8)	593 (1.7)
Dispensed prescriptions of anti-infectives, Prescribed Drug Register		
Number of dispensations in the first three days		
0	1,245 (99.8)	34,803 (99.8)
≥1	3 (0.2)	83 (0.2)
Number of dispensations in the first month		
0	1,232 (98.7)	34,447 (98.7)
≥1	16 (1.3)	439 (1.3)
Number of dispensations in the first year of life		
0	1,015 (81.3)	27,868 (79.9)
≥1	233 (18.7)	7,018 (20.1)

Supplementary Table 3. Sensitivity analysis restricted to first births only. Risk ratios for any infection in the first three days and in the first year of life comparing 559 infants born to mothers with SLE to 14,283 infants born to mothers from the general population, overall and by preterm birth

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Any infection in the first three days				
Overall	18/559 (3.2)	211/14,283 (1.5)	2.18 (1.36-3.50)	2.04 (1.26-3.30)
Term birth	8/475 (1.7)	161/13,474 (1.2)	1.41 (0.70-2.85)	1.27 (0.62-2.60)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	16/683 (2.3)	NE	NE
Very preterm birth (<32 weeks)	10/23 (43.5)	34/126 (27.0)	1.61 (0.93-2.79)	1.68 (0.97-2.93)
Any infection in the first month of life				
Overall	26/559 (4.6)	541/14,283 (3.8)	1.23 (0.84-1.80)	1.17 (0.80-1.73)
Term birth	15/475 (3.2)	475/13,474 (3.5)	0.90 (0.54-1.49)	0.85 (0.51-1.42)
Preterm birth (32 to 37 weeks)	1/61 (1.6)	30/683 (4.4)	0.37 (0.05-2.69)	0.36 (0.05-2.57)
Very preterm birth (<32 weeks)	10/23 (43.5)	36/126 (28.6)	1.52 (0.89-2.62)	1.58 (0.91-2.73)
Any infection in the first year of life				

Overall	173/559 (31.0)	4,460/12,283 (31.2)	0.99 (0.87-1.12)	1.06 (0.93-1.20)
Term birth	138/475 (29.1)	4,165/13,474 (30.9)	0.93 (0.81-1.08)	1.01 (0.88-1.17)
Preterm birth (32 to 37 weeks)	19/61 (31.2)	226/683 (33.1)	0.94 (0.64-1.39)	0.96 (0.65-1.41)
Very preterm birth (<32 weeks)	16/23 (69.6)	69/126 (54.8)	1.27 (0.93-1.74)	1.31 (0.95-1.80)
Hospitalized infection in the first three days				
Overall	5/559 (0.9)	89/14,283 (0.6)	1.44 (0.59-3.52)	1.36 (0.55-3.37)
Term birth	5/475 (1.1)	87/13,474 (0.7)	1.63 (0.67-4.00)	1.54 (0.62-3.84)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	2/683 (0.3)	NE	NE
Very preterm birth (<32 weeks)	0/23 (0.0)	0/126 (0.0)	NE	NE
Hospitalized infection in the first month of life				
Overall	8/559 (1.4)	150/14,283 (1.1)	1.36 (0.67-2.76)	1.28 (0.62-2.62)
Term birth	8/475 (1.7)	146/13,474 (1.1)	1.55 (0.77-3.15)	1.44 (0.70-2.96)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	4/683 (0.6)	NE	NE
Very preterm birth (<32 weeks)	0/23 (0.0)	0/126 (0.0)	NE	NE
Hospitalized infection in first year of life				
Overall	25/559 (4.5)	560/14,283 (3.9)	1.14 (0.77-1.69)	1.22 (0.82-1.81)

Term birth	21/475 (4.4)	509/13,474 (3.8)	1.17 (0.76, 1.79)	1.27 (0.83, 1.96)
Preterm birth (32 to 37 weeks)	2/61 (3.3)	38/683 (5.6)	0.59 (0.15-2.38)	0.60 (0.15-2.45)
Very preterm birth (<32 weeks)	2/23 (8.7)	13/126 (10.3)	0.84 (0.20-3.49)	0.98 (0.22-4.44)

Abbreviation: NE = not possible due to low number of events. Any infection is based on primary and secondary ICD-coded visits in the in- and outpatient databases of the National Patient Register and prescribed anti-infectives in the Prescribed Drug Register.
*Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

Supplementary Table 4. Sensitivity analyses restricted to A) first births only and B) mothers without an infection during pregnancy. Estimates of direct effects and effects mediated through preterm birth (<37 weeks gestation) of the association between maternal SLE and infections in infants in the first three days and in the first year of life*

Mediator: Preterm birth (<37 weeks) vs. full term	Direct effect	Indirect effect through preterm birth	Total effect	Mediated through preterm birth, % (95% CI)
A) First births only				
Any infection in the first 3 days of life	1.48 (0.68-2.28)	1.47 (1.06-1.87)	2.17 (1.05-3.29)	59 (19-98)
Any infection in the first year of life	1.02 (0.83-1.22)	1.06 (0.99-1.13)	1.08 (0.88-1.29)	77 (-117 – 272)
B) Mothers without infection during pregnancy				
Any infection in the first 3 days of life	1.16 (0.62, 1.70)	1.61 (1.20, 2.02)	2.87 (1.07, 2.67)	82 (33-130)
Any infection in the first year of life	1.07 (0.94, 1.21)	1.05 (1.00, 1.10)	1.13 (0.99, 1.27)	45 (-8-98)

* Values are odd ratios (95% confidence interval) which estimates risk ratios unless indicated otherwise. Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

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Title: The association between maternal systemic lupus erythematosus and infant infection: a population-based cohort study in Sweden

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Running title: Maternal SLE and infant infection risk

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ABSTRACT

Objectives: To investigate infection risk in offspring born to women with systemic lupus erythematosus (SLE) compared to offspring born to women without SLE, and examine the mediating role of preterm birth.

Design: Register-based cohort study.

Setting: Liveborn singletons born in Sweden, 2006-2021.

Participants: 1,248 infants born to mothers with SLE (≥2 ICD-coded visits in the National Patient Register (NPR) and Medical Birth Register, with ≥1 visit before pregnancy) and 34,886 infants born to women without SLE from the general population.

Primary and secondary outcome measures: Any visit for infection in the NPR or anti-infectives in the Prescribed Drug Register. The secondary outcome was hospitalized infection. Infection risks within 72 hours, within 1 month and within 1 year were estimated.

Results: SLE offspring had a higher risk of infection in the first 72 hours compared to non-SLE (2.1% vs. 1.2%; RR (95% CI) 1.62 (1.09 to 2.42)), the first month (5.2% vs. 4.5%; RR 1.12 (0.88 to 1.43)) and first year of life (38.2% vs. 37.2%; RR 1.09 (1.01 to 1.17)). The hospitalized infection risk for SLE offspring was similar to non-SLE (5.8% vs. 5.5%, first year of life). The percentage of the total effect of maternal SLE on infant infection mediated through preterm birth was 86% for infection in the first 72 hours and 27% in the first year of life.

Conclusions: The risk of infection in SLE offspring is most increased in the first three days after birth and a proportion of this association can be explained by preterm birth. To prevent early neonatal infections, maternal SLE could be considered as a risk factor before allowing early discharge from postnatal care.

Strengths and limitations of this study

- The use of prospectively collected, contemporary, population-based data from the entire Swedish population minimized selection bias and increased power.
- We were able to link infants to mothers with and without SLE and follow them for one year after birth by using each individual's unique personal identification number.
- Mothers with SLE might seek and/or receive more healthcare than mothers without SLE which would result in an overestimate of the association between maternal SLE and infant infection.
- The national registers used in this study do not capture information on lupus disease activity, clinical phenotype or, severity which might modify the risk of infant infection.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory autoimmune disease that predominantly affects women of childbearing age. Women with SLE have a 20-30% risk of preterm delivery which is two to three times higher than the risk among women without SLE.[1-5] The downstream effect of maternal SLE on infants is not as clear. A previous study from Sweden reported that 21% of infants born to women with SLE had an infection during their first year of life compared to 14% of infants born to mothers without SLE.[4] As the nature of this study was strictly descriptive, it remains unclear if the association between maternal SLE exposure during pregnancy and infections in infants is still present after considering confounding factors and the mediating effect of preterm birth.

Preterm birth (birth before 37 weeks of gestation), is likely an important mediator in the association between maternal SLE and infant infections. Being born preterm is a risk factor for infections, especially early-onset infections of which clinical manifestations usually appear within the first 72 hours.[6, 7] This is partly due to maternal infection (one cause of preterm birth) and immature organs (e.g. lungs and skin). Also, preterm infants often require prolonged intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms, placing them at increased risk for infections. [6, 7] Infants born preterm have on average 1.5 times the total number of infections in the first year of life compared to infants born full-term.[8]

The current study investigates the association between maternal SLE and the risk of infection in infants during the first year of life, and how much of the association can be explained by preterm birth. We used nationwide population-based registers in Sweden to compare infection risk in infants born to women with SLE to infants born to women without SLE.

METHODS

Study setting and sources

In Sweden, access to health care is universal and residents have a unique personal identification number that allows for the linkage of their records in registers. Maternal health during pregnancy, delivery, and neonatal outcomes of over 98% of deliveries in Sweden are registered in the Medical Birth Register (MBR) starting in 1973. Until July 2008, births ≥28 gestational weeks and live births were included. From July 2008, the MBR also included stillbirths ≥22 gestational weeks. Information on sex, year of birth, county of residence, and immigration, from 1968 onward was captured in the Total Population Register (TPR). Date of death is collected in the Cause of Death Register. Hospitalization data with national coverage from 1987 onward and non-primary care specialized outpatient visits since 2001 are captured in the National Patient Register (NPR). Primary and secondary diagnoses are listed for each visit using International Classification of Diseases (ICD) codes. Since July 2005, dispensed prescriptions of medications in the Swedish population are captured in the Prescribed Drug Register (PDR) using Anatomical Therapeutic Chemical (ATC) codes.

Study population

Infants born to mothers with SLE (exposed) and without SLE from the general population (unexposed) were identified by linking the NPR to the MBR. Women with ≥1 ICD-coded visits for SLE (ICD-10: M32, excluding M32.0 drug-induced lupus) in the inpatient or outpatient records of the NPR were matched to ten randomly sampled comparators from the general population without SLE, identified in the TPR, on year of birth, sex, calendar time, and residential location. We further restricted the women with SLE to have ≥2 visits listing SLE, at least one of which was required to be given at a department or specialist that diagnoses, treats or manages SLE (rheumatology, dermatology, nephrology, internal medicine and/or paediatrics). This definition is estimated to have a positive predictive value of 80% in women,[9] but its accuracy has not been evaluated for identifying pregnant women with prevalent SLE.

From this population of women with SLE and the general population comparators without SLE, we identified those who gave birth to a liveborn singleton registered in the MBR between March 2006 (as the PDR started in July 2005) and December 2021

without missing data on gestational age. A flow chart of the study population selection is depicted in Figure 1.

Maternal SLE at delivery

The infants were considered to be born to a mother with SLE if the mother had at least one SLE discharge code before pregnancy at a specialist clinic (rheumatology, dermatology, nephrology, internal medicine and/or paediatrics). The first observed SLE discharge code was used as a proxy for diagnosis date as it is the first observed diagnosis in our data, which does not include primary care. However, SLE diagnosis typically is given by specialists, therefore this is a reasonable proxy. Infants born to women with only one visit for SLE before delivery or with no visits with a specialist before pregnancy were excluded to minimise misclassification of maternal SLE. There were no general population comparators with an SLE discharge code before pregnancy. The study period was from the infant's date of birth for one year, death, or emigration, whichever came first. Ethical approval was granted by the Ethics Review Authority in Sweden (DNR 2021-01148).

Infections in infants

Any infant infection was identified using both primary and secondary ICD-coded visits in the inpatient and outpatient records of the NPR and dispensed prescriptions of anti-infectives in the PDR (the majority of which were antibiotics). We also examined hospitalized infections separately, defined as a hospitalization listing infection as the primary diagnosis in the inpatient records of the NPR. The first infection during follow-up was categorized into upper respiratory, lower respiratory, gastrointestinal, and other infections. For a list of ICD codes for infections and ATC codes for dispensed prescriptions of anti-infectives, see Supplementary Table 1, adapted from Sørup et al. (2016), Miller et al. (2016) and Bröms et al. (2020).[10-12] For any infection and hospitalized infection, we identified those occurring in the first three days (early-onset), within one month and within one year of birth. We examined infections in the first three days because it has a different pathogenesis than infections later in life and is associated with serious complications that can be life-threatening.

Preterm birth and other covariates

Preterm birth (birth before 37 weeks of gestation) and very preterm birth (birth before 32 weeks of gestation) were identified in the MBR. Additional data from the MBR included the infant's sex, infant's date of birth, parity (first or subsequent birth), gestational age in weeks, maternal age at delivery, and self-reported maternal first trimester smoking (yes/no/missing). Maternal height and weight collected at the first prenatal visit was used to calculate the body mass index (BMI) as weight divided by height squared (kg/m^2). Maternal infection during pregnancy was collected from the NPR and defined as an inpatient or outpatient visit listing an ICD code for infection.

Statistical analysis

Continuous variables were described using means and standard deviations (SD) and categorical variables were described with frequencies and column percentages. We calculated risk ratios (RR) and corresponding 95% confidence intervals using modified Poisson regression models to estimate the risk of infant infection comparing infants born to mothers with SLE to infants born to general population comparators.[13] Models were adjusted for maternal age at delivery (continuous), maternal fist-trimester smoking (yes/no/missing), and calendar year (continuous). RRs for any infant infection in three time windows were estimated: 1) within the first 72 hours, 2) the first month and 3) the first year of life, overall and by preterm birth. RRs were also estimated for hospitalized infection in the three time windows. In a sensitivity analysis, we reran all models among only first births. It has been shown that outcomes from the first pregnancy might be less favorable than subsequent pregnancies.[14]

We conducted a mediation analysis using a casual inference counterfactual approach to examine how much of the association between maternal SLE and any infection in infants could be explained by preterm birth.[15] Mediation analysis can be used to assess factors that are caused by the exposure (maternal SLE) and cause the outcome (infant infection) to better understand the relationship between exposure and outcome and to ultimately identify factors which can be intervened upon. Causal mediation analysis accommodates interaction between the exposure and mediator. We investigated the how much of the association between maternal SLE and infant infection operates through the mediating effect of preterm birth. Total effects were separated into natural direct effects and natural indirect effects through preterm birth. Results were reported on the odds ratio scale which estimates the RR and is

comparable with the RR. Based on knowledge from the literature, causal mediation models were adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous) to account for exposure-mediator, mediator-outcome, and exposure-outcome confounding.[16] We included an interaction between maternal SLE and preterm birth in the model. Because maternal infection is associated with both preterm birth and infant infection, we also performed a sensitivity analysis excluding mothers with an infection during pregnancy in a sensitivity analysis. All data management and analyses were performed using SAS, version 9.4.

RESULTS

Baseline characteristics of mothers and infants. We included 1,248 infants born to mothers with SLE and 34,886 infants born to general population comparators (Table 1). The proportion of births that were first born was higher among SLE-exposed infants compared to those infants born to mothers without SLE (44.7% versus 40.9%), and SLE-exposed infants were almost three times more likely to be born preterm (13.5% versus 4.6%). Mothers with SLE were less likely to smoke during the first trimester (4.2%) than general population comparators (5.1%). On average, maternal age at delivery and maternal BMI were comparable between mothers with SLE and general population comparators.

Table 1. Baseline characteristics of 1,248 infants born to women with systemic lupus erythematosus (SLE) and 34,886 infants born to general population comparators

	Infants born to mothers with SLE (n =1,248)	**Infants born to general population comparators (n =34,886)**
Female offspring, n (%)	640 (51.3)	16,926 (48.5)
Year of birth, n (%)		
2006-2011	370 (29.7)	15,381 (44.1)
2012-2017	400 (32.0)	10,911 (31.3)
2018-2021	478 (38.4)	8,594 (24.6)
First birth, n (%)	558 (44.7)	14,280 (40.9)
Gestational age, mean ± SD completed weeks	38.7 (2.5)	39.8 (1.8)
Term birth, n (%)	1,080 (86.4)	33,291 (95.4)
Preterm birth, n (%)	168 (13.5)	1,595 (4.6)
32-37 weeks of gestation	136 (10.9)	1,354 (3.9)
<32 weeks of gestation	32 (2.6)	241 (0.7)
Maternal age at delivery, years, mean ± SD	32.3 (4.6)	32.0 (5.0)
Maternal age at delivery in categories, years, n (%)		
<35	882 (70.7)	25,161 (72.1)
≥35	366 (29.3)	9,725 (27.9)
Maternal infection during pregnancy, n (%)	117 (9.4)	1358 (3.9)
Maternal body mass index, mean ± SD *	24.4 (4.3)	24.9 (4.7)
Missing data on body mass index, n (%)	100 (8.0)	2,223 (6.4)
Maternal smoking during first trimester, n (%) *	53 (4.2)	1,763 (5.1)
Missing data on first-trimester smoking, n (%)	71 (5.7)	1,767 (5.1)

SD standard deviation; SLE systematic lupus erythematosus
*Mean or percentage exclude missing values

Risk of infant infections. Twenty-six (2.1%) infants born to mothers with SLE and 414 (1.2%) infants born to mothers without SLE were diagnosed with any infection in the first 72 hours of life (Table 2). The most common first registered infection in the first year of life was upper respiratory (SLE: 13.9% and non-SLE: 12.9%; Supplementary Table 2).

The risk of infection in the first 72 hours associated with maternal SLE was 63% higher than infants born to mothers without SLE (adjusted RR 1.63 [95% CI 1.09-2.42]). The RR for any infection in the first month of life was 1.12 [95%CI 0.88, 1.43] and results did not differ greatly when stratified by preterm birth (Table 2). When examining up to one year after birth, the risk of any infection was significantly higher in infants born to mothers with SLE (38.3%) than in infants born to mothers without SLE (37.2%), with a corresponding adjusted RR of 1.09 [95% CI 1.01-1.17].

In the first 72 hours, there was a higher percentage of infants born very preterm with an infection to mothers with SLE (11/32, 34.4%) than to mothers without SLE (63/241, 26.1%), although the corresponding RR was not significantly higher (1.32 [95%CI 0.77-2.25]; Table 2). Results among term and preterm births were similar to the overall estimates for the other time windows.

Seventy-three (5.8%) infants born to mothers with SLE and 1,923 (5.5%) infants born to mothers without SLE were hospitalized for infections in the first year of life, and 6 (0.5%) and 162 (0.5%) of those respectively occurred in the first three days (Table 3). Overall, the number of hospitalized infections was too small to stratify by preterm birth.

All the results remained similar to the main results in a sensitivity analysis including only first births, although with limited power for some subgroups (Supplementary Table 3).

Table 2. Risk ratios for any infection in the first year of life comparing infants born to mothers with systemic lupus erythematosus (SLE) to infants born to mothers from the general population, overall and by preterm birth.

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Any infection in the first three days				
Overall	26/1,248 (2.1)	414/34,886 (1.2)	1.75 (1.19-2.60)	1.63 (1.09-2.42)
Term birth	11/1,083 (1.0)	313/33,291 (0.9)	1.08 (0.60-1.97)	0.98 (0.53-1.80)
Preterm birth (32 to 37 weeks)	4/136 (2.9)	38/1,354 (2.8)	1.05 (0.38-2.89)	1.01 (0.36-2.79)
Very preterm birth (<32 weeks)	11/32 (34.4)	63/241 (26.1)	1.32 (0.78-2.22)	1.32 (0.77-2.25)
Any infection in the first month of life				
Overall	65/1,248 (5.2)	1,586/34,886 (4.5)	1.15 (0.90-1.46)	1.12 (0.88-1.43)
Term birth	44/1,080 (4.1)	1,436/33,291 (4.3)	0.94 (0.70-1.27)	0.92 (0.68-1.23)
Preterm birth (32 to 37 weeks)	10/136 (7.4)	80/1,354 (5.9)	1.24 (0.66-2.34)	1.18 (0.62-2.26)
Very preterm birth (<32 weeks)	11/32 (34.4)	70/241 (29.1)	1.18 (0.71-1.99)	1.19 (0.71-2.02)
Any infection in the first year of life				
Overall	478/1,248 (38.3)	12,985/34,886 (37.2)	1.03 (0.96-1.11)	1.09 (1.01-1.17)
Term birth	400/1,080 (37.0)	12,270/33,291 (36.9)	1.00 (0.93-1.09)	1.07 (0.99-1.16)

Preterm birth (32 to 37 weeks)	59/136 (42.4)	569/1,354 (42.0)	1.03 (0.84-1.26)	1.06 (0.86-1.29)
Very preterm birth (<32 weeks)	19/32 (59.4)	146/241 (60.6)	0.98 (0.72-1.33)	0.99 (0.73-1.35)

Any infection is defined as a visit listing an ICD code for infection as primary or secondary diagnosis in the inpatient or outpatient components of the National Patient Register or a dispensed anti-infective listed in the Prescribed Drug Register.

*Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

Table 3. Risk ratios for hospitalized infection in the first year of life comparing infants born to mothers with systemic lupus erythematosus (SLE) to infants born to mothers from the general population, overall and by preterm birth.

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Hospitalized infection in the first three days				
Overall	6/1,248 (0.5)	162/34,886 (0.5)	1.04 (0.46-2.33)	0.97 (0.43-2.23)
Term birth	5/1,080 (0.5)	159/33,291 (0.5)	0.97 (0.40-2.36)	0.91 (0.37-2.22)
Preterm birth (32 to 37 weeks)	1/136 (0.7)	3/1,354 (0.2)	NE	NE
Very preterm birth (<32 weeks)	0/32 (0.0)	0/241 (0.0)	NE	NE
Hospitalized infection in the first month of life				
Overall	22/1,248 (1.8)	485/34,886 (1.4)	1.27 (0.83-1.94)	1.25 (0.81-1.91)
Term birth	19/1,080 (1.8)	473/33,291 (1.4)	1.24 (0.79-1.95)	1.21 (0.77-1.92)
Preterm birth (32 to 37 weeks)	3/136 (2.2)	12/1,354 (0.9)	NE	NE
Very preterm birth (<32 weeks)	0/32 (0.0)	0/241 (0.0)	NE	NE
Hospitalized infection in first year of life				
Overall	73/1,248 (5.8)	1,923/34,886 (5.5)	1.06 (0.85-1.33)	1.13 (0.90-1.42)
Term birth	59/1,080 (5.5)	1,776/33,291 (5.3)	1.02 (0.80-1.32)	1.10 (0.85-1.41)

Preterm birth (32 to 37 weeks)	11/136 (8.1)	110/1,354 (8.1)	1.00 (0.55-1.80)	1.03 (0.56-1.88)
Very preterm birth (<32 weeks)	3/32 (9.4)	37/241 (15.4)	0.61 (0.20-1.87)	0.64 (0.20-1.97)

Abbreviation: NE = not estimatable due to low number of events.

Hospitalized infections are an ICD-coded visits lisiting infection as the primary diagnosis in the inpatient component of the National Patient Register.

*Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

The mediating role of preterm birth. Considering all births, 85% (95%CI 27-144) of the association between maternal SLE and any infection in the first three days of life was mediated by preterm birth (Table 4). The proportion mediated through preterm birth for the first year of life was 28% (95%CI -10-66). Looking at first births only, the proportion mediated was 59% (95%CI 19-98) for any infection in the first three days and 77% (95%CI -117-272) in the first year (Supplementary Table 4). A small proportion of mothers had a visit in inpatient or outpatient care listing an ICD code for infection during pregnancy (9.4% SLE, 3.9% general population), and excluding these pregnancies did not considerably change the estimates in mediation analyses (Supplementary Table 4).

Table 4. Estimates of the mediating effect of preterm birth (<37 weeks gestation) in the association between maternal SLE and infant infections within the first three days and the first year of life. Direct, indirect and total effects are estimated with odds ratios and 95% confidence intervals (OR 95%CI).

Mediator: Preterm birth vs. full term	Direct effect OR (95%CI)	Indirect effect through preterm birth OR (95%CI)	Total effect OR 95%CI	% Mediated through preterm birth (95% CI)
Outcome				
Any infection in the first 3 days of life	1.10 (0.60-1.61)	1.55 (1.18-1.93)	1.71 (1.00-2.43)	85 (27-144)
Any infection in the first year of life	1.10 (0.97-1.23)	1.03 (0.99-1.07)	1.13 (1.00-1.27)	28 (-10 - 66)

OR odds ratio; CI confidence interval. Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

DISCUSSION

In this population-based study in Sweden, infants born to mothers with SLE had a 63% increased risk of any infection in the first three days of life compared with infants born to general population comparators. In the first year of life, the risk of any infection in infants born to mothers with SLE was 9% higher than infants who were not exposed to maternal SLE. Being born preterm accounted for a proportion of the association between maternal SLE and any infection in the first three days of life. We did not find a significant association between maternal SLE and hospitalized infection at any time point in the first year of life.

Information on the risk of infections in infants exposed to maternal SLE during pregnancy is limited. In a previous descriptive study of SLE pregnancies in Sweden using the same data sources but with data only through 2012, the one-year infection risk was significantly higher in infants born to women with SLE compared to infants born to general population comparators.[4] In contrast, we used a broader definition of infections with more ICD-10 codes and anti-infective medications for systemic use and births through 2021. Ignacio and colleagues reported risks of infant infections associated with exposure to maternal SLE, with the risk of any infection in the first 30 days of life of 3.9% in SLE-exposed infants and 2.3% in unexposed infants born to general population comparators.[17] In comparison, we observed a slightly higher risk of infection in both SLE (5.2%) and general population (4.5%) for the same time period.

Women with SLE in our study were three times more likely to deliver preterm than their general population comparators, which has been reported by others.[4, 5, 18] Mediation analysis showed that preterm birth explained a proportion of the association between infection in the first three days of life and maternal SLE. Maternal infection is a risk factor for preterm birth, and also for neonatal infection, and the SLE mothers had a higher prevalence of infection during pregnancy compared to the general population.(7) However, when pregnancies with a maternal infection-related hospitalization or outpatient specialst visit were excluded, estimates remained similar to the main analysis. We cannot exclude the possibility that there is residual confounding related to maternal infection or other unmeasured confounders and therefore these results should be interpreted cautiously. We are most likely not capturing all maternal infections by using ICD-coded visits. Efforts to decrease infant infection should focus on preventing preterm delivery when possible. Maternal SLE

should be considered a risk factor for early neonatal infections and could be used to assess risk when considering early hospital discharge.

The current study has several strengths. We used a register-based linkage of prospectively collected, population-based data of the entire Swedish population and their infants including the most up-to-date data with follow-up until December 31, 2022. We used a register-based definition of SLE which has good validity.[19] Also, the results of this study can be generalizable to populations with universal access to health care.

We realize that our study has also several limitations. We do not have information on breastfeeding, which is associated with a lower risk of respiratory infections with fever, middle ear infection, and infective gastroenteritis in infants.[20] Women with SLE may breastfeed their infants less, especially those born preterm, than general population comparators. While most SLE medications are likely safe in breastfeeding, worries about medication use is an important reason for women with SLE not to breastfeed.[21, 22] Also, there is evidence that infants exposed to maternal SLE born preterm are less likely to be breastfed than babies born at term.[21, 22] Mothers with SLE might seek and/or receive more healthcare than mothers without SLE which would result in more registered outpatient infections and more prescriptions of anti-infectives. By using ICD- and ATC-codes to identify infant infections, the exact cause of the infection is not clear as we did not have access to laboratory results and not all infants may have received a laboratory test for type of infection. The national registers do not capture information on disease activity, clinical phenotype or severity and thus were not accounted for in this study. Lupus disease activity is an important risk factor for pregnancy complications including preterm delivery.[23] Lupus disease activity and phenotype are strongly related to medication use, and all of these factors could affect infant infection. We do not have information on rituximab use during pregnancy, which depletes B cells in the mother and baby and affects infant infection risk. However, during the study's time period rituximab was not recommended for use during pregnancy, except in extremely rare cases, according to treatment guidelines by the Swedish Society of Rheumatology. Therefore we do not believe that rituximab has greatly affected our results. Future studies should investigate the relationship between SLE-related characteristics and infant infection with more clinically detailed data, with a focus on preterm infants who carry the majority of the risk. Some analyses were

limited in power, resulting in wide confidence intervals and the proportion mediated estimates are unstable when sample sizes are small.[24] Although we adjusted for several confounders of the exposure-mediator and mediator-outcome relationships, there is likely to be residual confounding.

In conclusion, the risk of infection in infants born to mothers with SLE is slightly increased during the first year of life. The relative risk is highest during the first days after birth, and some of the increased risk was accounted for by preterm birth. The role of maternal infection, immune dysfunction and/or inflammation should be clarified in future studies. Our findings underscore the importance of preventing preterm delivery whenever possible, but preterm delivery may not be avoidable in some circumstances and it is sometimes necessary for the health of the mother and infant. Therefore, to prevent early neonatal infections, maternal SLE could be considered as a risk factor before allowing early discharge from postnatal care. Awareness about the higher infection risk in the first weeks of life, avoiding crowds and people with infections, and vigilance about infection symptoms, should perhaps be recommended to mothers with SLE.

Competing interests

The authors declare no competing interests.

Contributorship

EA is responsible for the overall content as guarantor. SG, EA and JS designed the study and analysis plan with input from MA and ES. SG and EA conducted the data analysis. SG wrote the first draft of the manuscript and EA, JS, MA and ES provided substantive input to revise and finalise the manuscript.

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Ethical approval

Ethics Review Authority in Sweden, decision no. 2021-01148. The need for consent was waived by the ethics committee and data were anonymised prior to being accessed by the study authors.

Data sharing statement

The individual-level data used in this study cannot be publicly made available due to legal restrictions. Please send any requests for the study data to the corresponding author.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of this study.

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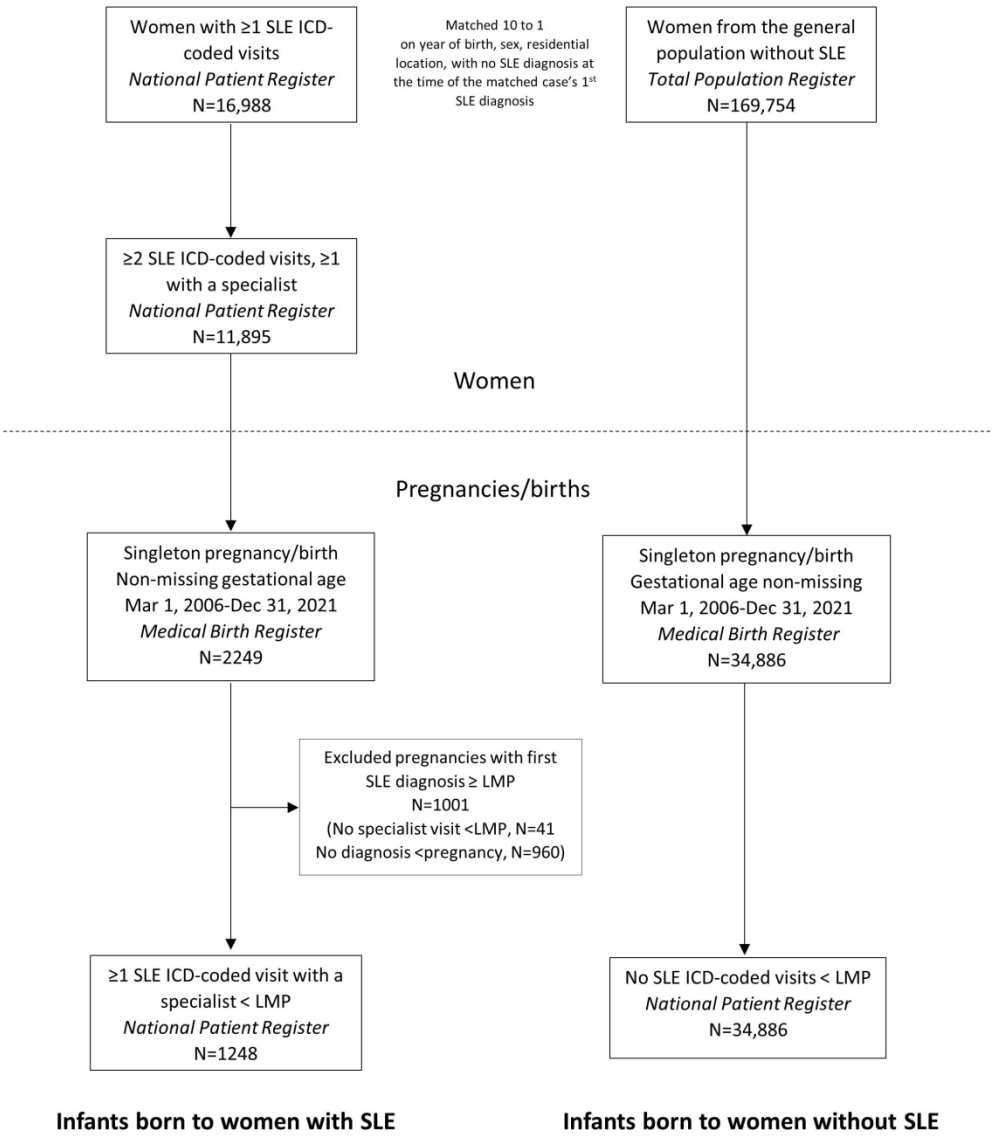
Figure Legend

Figure 1. Flow chart of study population selection.



Flow chart of study population selection

190x229mm (300 x 300 DPI)

Supplementary Table 1. International classification of disease (ICD) codes used to define infections and anatomical therapeutic chemical (ATC) classification codes used to define treatment for infections in infants.

		ICD-10 (1997-2021)
Upper respiratory	Ear	H60.1-H60.3, H65-H67, H70
	Sinusitis	J01
	Pharyngitis	J02, J39.1, J39.2
	Tonsillitis	J03
	Laryngitis	J04, J05
	Upper respiratory infection, unspecified sites	J06
	Influenza	J09-J11
	Peritonsillar abscess	J36
Lower respiratory	Viral pneumonia	J12
	Pneumonia	J13-J18
	Other, including whooping cough	A37, J20-J22, J85, J86
Gastrointestinal	Intestinal infectious diseases	A00-A09
		K04.0, K04.4, K04.7, K05.0, K05.2, K11.3, K12.2, K35-K37, K61
Other	Erysipelas, lymphadenitis, infections of the skin and subcutaneous tissue	A46, H60.0, L00-L08
	Bacterial infections	A20-A28, A30-A36, A38-A39, A43-A44, A48-A54, A65-A79, B95-B97
	Bacterial sepsis, meningitis and other infections of perinatal period	A40-A41, G00-G01, G03-G04, G06-G09, P36-P39
	Tuberculosis	A15-A19
	Mycoses	A42, B35-B49
	Urinary tract	N13.6, N30.0, N39.0
	Circulatory system	I00, I01, I30.1, I33, I40.0, I41.0, I43.0, I52.0

	Musculoskeletal	M00, M01, M46.2-M46.5M72.6, M86
	Tropical	B50-B83, B85-B94
	Encephalitis, rabies, poliomyelitis, meningitis	A80-A89, G02, G05
	Other viral	A60, A63, A90-A96, A98, A99, B00-B02, B04-B06, B08, B09, B15-B19, B25-B27, B30, B33, B34, B97
	Congenital viral diseases	P35
		ATC codes
Treatment for infection	Anti-infective for systemic use	J01, J02, J04, J05

Supplementary Table 2. Number and type of infections and dispensed prescriptions of antibiotics in the first three months of life in 1,248 infants born to women with systemic lupus erythematosus and 34,886 infants born to general population comparators

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)
Primary and Secondary Outpatient infections, National Patient Register		
Number of infections in the first three days		
0	1,248 (100.0)	34,881 (100.0)
≥1	0 (0.0)	5 (0.0)
Number of infections in the first month		
0	1,228 (98.4)	34,057 (97.6)
≥1	20 (1.6)	829 (2.4)
Number of infections in the first year of life		
0	900 (72.1)	25,926 (74.3)
≥1	348 (27.9)	8,960 (25.7)
Type of first infection in the first year of life		
Upper respiratory	174 (13.9)	4,509 (12.9)
Lower respiratory	45 (3.6)	834 (2.4)
Gastrointestinal	25 (2.0)	786 (2.3)
Other	104 (8.3)	2831 (8.1)
Primary and Secondary Hospitalized infections, National Patient Register		
Number of infections in the first three days		
0	1,225 (98.2)	34,550 (99.0)
≥1	23 (1.8)	336 (1.0)
Number of infections in the first month		
0	1,203 (96.4)	34,190 (98.0)
≥1	45 (3.6)	696 (2.0)
Number of infections in the first year of life		
0	1,145 (91.7)	32,651 (93.6)
≥1	103 (8.3)	2,235 (6.4)
Type of first infection in the first year of life		
Upper respiratory	15 (1.2)	403 (1.0)

Lower respiratory	31 (2.5)	693 (2.0)
Gastrointestinal	7 (0.6)	286 (0.8)
Other	50 (4.0)	853 (1.7)
Only Primary Hospitalized Infections, National Patient Register		
Number of infections in the first three days		
0	1,242 (99.5)	34,724 (99.5)
≥1	6 (0.5)	162 (0.5)
Number of infections in the first month		
0	1,226 (98.2)	34,401 (98.6)
≥1	22 (1.8)	485 (1.4)
Number of infections in the first year of life		
0	1,176 (94.2)	32,998 (94.6)
≥1	72 (5.8)	1,888 (5.4)
Type of first infection in the first year of life		
Upper respiratory	12 (1.0)	342 (1.0)
Lower respiratory	31 (2.5)	686 (2.0)
Gastrointestinal	6 (0.5)	267 (0.8)
Other	23 (1.8)	593 (1.7)
Dispensed prescriptions of anti-infectives, Prescribed Drug Register		
Number of dispensations in the first three days		
0	1,245 (99.8)	34,803 (99.8)
≥1	3 (0.2)	83 (0.2)
Number of dispensations in the first month		
0	1,232 (98.7)	34,447 (98.7)
≥1	16 (1.3)	439 (1.3)
Number of dispensations in the first year of life		
0	1,015 (81.3)	27,868 (79.9)
≥1	233 (18.7)	7,018 (20.1)

Supplementary Table 3. Sensitivity analysis restricted to first births only. Risk ratios for any infection in the first three days and in the first year of life comparing 559 infants born to mothers with SLE to 14,283 infants born to mothers from the general population, overall and by preterm birth

	Infants born to mothers with SLE, no. cases/total (%)	Infants born to general population comparators, no. cases/total (%)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Any infection in the first three days				
Overall	18/559 (3.2)	211/14,283 (1.5)	2.18 (1.36-3.50)	2.04 (1.26-3.30)
Term birth	8/475 (1.7)	161/13,474 (1.2)	1.41 (0.70-2.85)	1.27 (0.62-2.60)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	16/683 (2.3)	NE	NE
Very preterm birth (<32 weeks)	10/23 (43.5)	34/126 (27.0)	1.61 (0.93-2.79)	1.68 (0.97-2.93)
Any infection in the first month of life				
Overall	26/559 (4.6)	541/14,283 (3.8)	1.23 (0.84-1.80)	1.17 (0.80-1.73)
Term birth	15/475 (3.2)	475/13,474 (3.5)	0.90 (0.54-1.49)	0.85 (0.51-1.42)
Preterm birth (32 to 37 weeks)	1/61 (1.6)	30/683 (4.4)	0.37 (0.05-2.69)	0.36 (0.05-2.57)
Very preterm birth (<32 weeks)	10/23 (43.5)	36/126 (28.6)	1.52 (0.89-2.62)	1.58 (0.91-2.73)
Any infection in the first year of life				

Overall	173/559 (31.0)	4,460/12,283 (31.2)	0.99 (0.87-1.12)	1.06 (0.93-1.20)
Term birth	138/475 (29.1)	4,165/13,474 (30.9)	0.93 (0.81-1.08)	1.01 (0.88-1.17)
Preterm birth (32 to 37 weeks)	19/61 (31.2)	226/683 (33.1)	0.94 (0.64-1.39)	0.96 (0.65-1.41)
Very preterm birth (<32 weeks)	16/23 (69.6)	69/126 (54.8)	1.27 (0.93-1.74)	1.31 (0.95-1.80)
Hospitalized infection in the first three days				
Overall	5/559 (0.9)	89/14,283 (0.6)	1.44 (0.59-3.52)	1.36 (0.55-3.37)
Term birth	5/475 (1.1)	87/13,474 (0.7)	1.63 (0.67-4.00)	1.54 (0.62-3.84)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	2/683 (0.3)	NE	NE
Very preterm birth (<32 weeks)	0/23 (0.0)	0/126 (0.0)	NE	NE
Hospitalized infection in the first month of life				
Overall	8/559 (1.4)	150/14,283 (1.1)	1.36 (0.67-2.76)	1.28 (0.62-2.62)
Term birth	8/475 (1.7)	146/13,474 (1.1)	1.55 (0.77-3.15)	1.44 (0.70-2.96)
Preterm birth (32 to 37 weeks)	0/61 (0.0)	4/683 (0.6)	NE	NE
Very preterm birth (<32 weeks)	0/23 (0.0)	0/126 (0.0)	NE	NE
Hospitalized infection in first year of life				
Overall	25/559 (4.5)	560/14,283 (3.9)	1.14 (0.77-1.69)	1.22 (0.82-1.81)

Term birth	21/475 (4.4)	509/13,474 (3.8)	1.17 (0.76, 1.79)	1.27 (0.83, 1.96)
Preterm birth (32 to 37 weeks)	2/61 (3.3)	38/683 (5.6)	0.59 (0.15-2.38)	0.60 (0.15-2.45)
Very preterm birth (<32 weeks)	2/23 (8.7)	13/126 (10.3)	0.84 (0.20-3.49)	0.98 (0.22-4.44)

Abbreviation: NE = not possible due to low number of events. Any infection is based on primary and secondary ICD-coded visits in the in- and outpatient databases of the National Patient Register and prescribed anti-infectives in the Prescribed Drug Register.
*Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).

Supplementary Table 4. Sensitivity analyses restricted to A) first births only and B) mothers without an infection during pregnancy. Estimates of direct effects and effects mediated through preterm birth (<37 weeks gestation) of the association between maternal SLE and infections in infants in the first three days and in the first year of life*

Mediator: Preterm birth (<37 weeks) vs. full term	Direct effect	Indirect effect through preterm birth	Total effect	Mediated through preterm birth, % (95% CI)
A) First births only				
Any infection in the first 3 days of life	1.48 (0.68-2.28)	1.47 (1.06-1.87)	2.17 (1.05-3.29)	59 (19-98)
Any infection in the first year of life	1.02 (0.83-1.22)	1.06 (0.99-1.13)	1.08 (0.88-1.29)	77 (-117 – 272)
B) Mothers without infection during pregnancy				
Any infection in the first 3 days of life	1.16 (0.62, 1.70)	1.61 (1.20, 2.02)	1.87 (1.07, 2.67)	82 (33-130)
Any infection in the first year of life	1.07 (0.94, 1.21)	1.05 (1.00, 1.10)	1.13 (0.99, 1.27)	45 (-8-98)

* Values are odd ratios (95% confidence interval) which estimates risk ratios unless indicated otherwise. Models are adjusted for maternal age at delivery (continuous), maternal first-trimester smoking (yes/no/missing), and calendar year (continuous).