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# Early-onset preeclampsia in lupus pregnancy

**Julia F Simard**[1,2,3], **Elizabeth V Arkema**[3], **Cathina Nguyen**[1], **Elisabet Svenungsson**[4], **Anna-Karin Wikstrom**[3,5], **Kristin Palmsten**[6], and **Jane E Salmon**[7]

[1]Division of Epidemiology, Department of Health Research and Policy, Stanford School of Medicine, Stanford, CA

[2]Division of Immunology and Rheumatology, Department of Medicine, Stanford School of Medicine, Stanford, CA

[3]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden

[4]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden

[5]Department of Clinical Sciences, Karolinska Institute, Danderyd Hospital, Stockholm, Sweden

[6]Department of Pediatrics, University of California, San Diego, La Jolla, CA

[7]Division of Rheumatology, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY

## Abstract

**Background—**Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that occurs during childbearing years and has been associated with preeclampsia. However, little is known about preeclampsia of early onset, which is associated with severe adverse maternal and perinatal outcomes.

**Methods—**Using national population-based Swedish registers we identified women with SLE (≥2 visits with corresponding ICD-codes) and a sample without SLE who gave birth to singleton infants 2001-2012. Risk ratios (RR) and 95% confidence intervals (CI) for early-onset preeclampsia (defined by ICD-codes corresponding to preeclampsia registered at <34 weeks) in SLE women were calculated based on adjusted modified Poisson models for first, subsequent, and all pregnancies.

**Result—**Among 742 births to women with SLE and 10 484 births to non-SLE women there were 32 (4.3%) and 55 (0.5%) diagnoses of early-onset preeclampsia, respectively. SLE was associated with an increased risk of early-onset preeclampsia (RR 7.8, 95% CI 4.8, 12.9, all pregnancies). The association remained similar upon restriction to women without pregestational hypertension. Adjustment for antiphospholipid syndrome (APS)-proxy attenuated the association. RRs for early-

Corresponding Author Julia F Simard, Division of Epidemiology, Department of Health Research and Policy, Stanford School of Medicine, 259 Campus Drive, Stanford, CA 94305-5405, jsimard@stanford.edu.

**Competing Interests**

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onset preeclampsia were smaller for subsequent pregnancies (RR 4.7, 95% CI 2.0, 11.2) compared to first and all (see above).

**Conclusion—**Women with SLE are at increased risk of early-onset preeclampsia and this increased risk may be independent of the traditional risk factors pregestational hypertension, APS, BMI, or smoking. Women with SLE during pregnancy should be closely monitored for early-onset preeclampsia and future research needs to identify the non-traditional preeclampsia factors that might cause this serious outcome.

### Keywords

early preeclampsia; systemic lupus; pregnancy; registers

## Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory systemic autoimmune disease that disproportionately affects women with a peak in incidence during their childbearing years. Using Swedish population registers, the prevalence of SLE among women ages 15-49 was approximately 100 per 100,000 in 2010.[1] Women with SLE have between a two- and four-fold higher risk of preeclampsia during pregnancy.[2, 3] Less is known about the risk of early-onset preeclampsia in SLE, which is associated with worse outcomes in mother and child and may be biologically distinct from later-onset preeclampsia.[4] Placental abruption, stroke, acute respiratory distress, and perinatal death are more common in early-onset preeclampsia in comparison to later onset preeclampsia.[5]

Early-onset preeclampsia presents before 34 weeks gestation and is characterized by abnormal placentation and endothelial dysfunction, which may be due to an imbalance of angiogenic factors early in the pregnancy.[4] Interferon alpha (IFNα), a cytokine implicated in the pathogenesis of SLE, has antiangiogenic properties, is associated with vascular damage in SLE and has been implicated in the vulnerability of SLE patients to preeclampsia.[6]

Using a population-based cohort of women with SLE and general population comparators, we examined the relative risk of early-onset preeclampsia. Because early-onset preeclampsia is also associated with a decreased likelihood of additional pregnancies, and previous preeclampsia is associated with subsequent preeclampsia, we examined first and subsequent pregnancies separately.[7] We further examined whether the risk was increased among those women with no history of pregestational hypertension, a known risk factor for preeclampsia.

## Methods

### Study population and data sources

We restricted the study to women from the Swedish Lupus Linkage (SLINK) cohort with at least one pregnancy/birth registered in the Medical Birth Register (MBR) between October 2001 and December 2012. Briefly, the SLINK cohort includes all individuals in Sweden seeking care in inpatient or specialist outpatient care for SLE identified in the National Patient Register (NPR) and a sample of five randomly selected non-SLE individuals from the general population matched on birth year (age), sex, and county of residence at the time

the case was first identified.[8] Individuals in the non-SLE comparator group who present with an SLE diagnosis in the registers between their initial inclusion and the start of the present study (pregnancy) are excluded. We used all available SLE and non-SLE data from SLINK. The Prescribed Drug Register includes data on all medication dispensing throughout Sweden starting July 2005 but does not systematically capture medications administered during clinical visits, infusions, inpatient stays, or over the counter purchases.

The MBR includes prospectively collected information, including demographic data, reproductive history and complications during pregnancy, delivery and the neonatal period, on nearly all live births in Sweden gestational age 22 weeks or greater. Stillbirths are included from 28 weeks' gestation until July 2008 and from 22 weeks or greater thereafter. In Sweden, prenatal care is standardised and free of charge. During the first prenatal visit, usually at the end of the first trimester, women are interviewed about their medical and obstetric history, including height, smoking, and medication use, and their weight measured. Data on every pregnancy and delivery is forwarded to the MBR through copies of standardised prenatal, obstetric and pediatric records. Individual record linkage of our study population to these registers is possible through each individual's unique personal registration number, assigned to each Swedish resident.[9] We restricted to singleton births only. Ethical approval was provided by the Regional Ethics Board in Stockholm (DNR: 2011/920-31/1) and approved by Stanford University.

## Systemic lupus erythematosus definition

SLE was defined as at least two visits in the NPR (inpatient and outpatient non-specialist care) with an SLE ICD code, with at least one SLE-coded visit from a specialist (rheumatology, dermatology, nephrology, internal medicine, pediatrics). Previously in these register data we have demonstrated good face validity of our present SLE definition and found little misclassification when using supervised learning methods against nearly 1000 clinically confirmed cases from four rheumatology clinics in Sweden.[1, 10] If SLE was listed in the MBR or NPR before the baby's date of birth, the respective pregnancy was classified as maternal SLE exposed (i.e., the woman had prevalent SLE at the time of pregnancy and birth).

Unexposed individuals and pregnancies were a sample of non-SLE individuals from the SLINK cohort. These women had no ICD-coded visit with SLE in the NPR or MBR before the birth.

## Early-onset preeclampsia

The primary outcome, early-onset preeclampsia, was identified using the NPR for each pregnancy (ICD 10 O14 - O15) presenting before 34 weeks' gestational age in 2001-2012 using the date of visit from the NPR at preeclampsia diagnosis. Preeclampsia diagnosed at any time during pregnancy (early or late) from the NPR was included as a secondary outcome. Swedish clinical guidelines define preeclampsia during the study period as a blood pressure of ≥140/90 combined with proteinuria (≥0.3 g in 24 hours or 1 or more on a urine dipstick on at least 2 subsequent occasions).

### Additional covariates

Date of the last menstrual period (LMP) and gestational age were primarily estimated by early second trimester ultrasound. Maternal age was obtained from the MBR and included as a continuous variable in years. To account for the potential J-shaped association between age and preeclampsia, age was also included as a quadratic term. Body mass index (BMI) was calculated from weight and height registered at the first prenatal visit. Obesity was defined as BMI of 30 or greater ($kg/m^2$). Self-reported first trimester smoking was obtained from the MBR and dichotomized as yes/no. Pregestational hypertension was defined as present if there was any history of antihypertensive medication dispensing (ATC codes CO2A and CO2CA; after July 2005) or inpatient or outpatient visit with the discharge diagnoses coded in the NPR. Pregestational diabetes was similarly defined using the NPR and searching PDR for diabetes-related medications.

### Statistical analysis

Statistical analyses were performed for first, subsequent (second and more) and all pregnancies separately. We also examined these associations by type of preeclampsia (early-onset and all) from October 2001 through December 2012. The association between maternal SLE and early-onset preeclampsia was estimated by risk ratio (RR) and 95% confidence interval (CI) using modified Poisson models.[11] In analyses where women could contribute more than one pregnancies, the lack of independence was accounted for in the models using robust variance estimates. We adjusted for maternal age and the potential *a priori* confounders smoking, and pregestational hypertension and diabetes. The quadratic term for age was not significant and was not included in final models.

Missing data on smoking was handled multiple ways – first using the missing indicator method and second by a series of single imputations where the missing values were replaced with the extreme values to evaluate the robustness of the SLE – preeclampsia association. In this second approach we first assumed that all missing values were, for example, all non-smokers and then repeated the analysis recoding all missing values as smokers. Because pregestational hypertension is a strong risk factor for preeclampsia, we restricted to women without pregestational hypertension due to limited power.

### Sensitivity analysis

We conducted a series of sensitivity analyses. First we extended the definition of pregestational hypertension to include a dispensing from the PDR with any beta blocking agents, calcium channel blockers, or agents acting on the renin-angiotensin system (ATC: C07, C08, C09, respectively) before the estimated LMP. Second we excluded women with any care from a nephrology clinic or department (outpatient specialist care or consultation in the inpatient register during a hospitalization) in the year before LMP to reduce the potential misclassification of lupus nephritis as preeclampsia. Third, we adjusted for antiphospholipid syndrome (APS) to address potential uncontrolled confounding by APS in our main analysis. Using the subset of data with prescription information (2006-2012), we defined APS as presence of either ICD-10 code D68.6 or at least one heparin dispensing during pregnancy. Data were unavailable to distinguish between APS and anti-phospholipid (aPL) antibody positivity and little is known about validity of ICD codes to identify these

conditions. However, we also reran the full models including only the ICD-10 codes to identify APS to account for misclassification of history of deep vein thrombosis, thrombophilia, and other indications for antenatal heparin use other than APS.

## Results

Between October 2001 and December 2012 there were 742 women with SLE (343 first pregnancies in the MBR) and 10 484 women from the general population (4443 first pregnancies). The distribution of pre-pregnancy comorbidities was different across all comparison groups (Table 1). Women with SLE were more likely to have pregestational hypertension and diabetes compared to general population controls for first, subsequent, and all pregnancies. On average, women with lupus presented with preeclampsia earlier in their pregnancies (34.5 vs 37.0 weeks) compared to the general population. Pregestational hypertension and APS were most common in early-onset preeclampsia, although still relatively rare overall (3.5% and 1.2%, respectively; Table 2). Among the 32 pregnancies with early-onset preeclampsia to women with SLE, 75% were registered as first pregnancies and 34% either had APS coded or were dispensed low molecular weight heparin during pregnancy. Thirteen of these 32 (41%) had one or more of the commonly established risk factors for preeclampsia (obesity, pregestational hypertension, APS).

Compared to the general population, SLE during pregnancy was associated with a significantly increased risk of early-onset preeclampsia for all, first, and subsequent pregnancies, although confidence intervals were wide (RR 7.8, 95% CI 4.8, 12.9, all; Table 3). Lupus was associated with a nearly 4.5-fold increased risk of early-onset preeclampsia controlling for maternal age, smoking, and pregestational diabetes and hypertension, (RR 4.7, 95% CI 2.0, 11.2) when looking at subsequent pregnancies only. SLE exposure during pregnancy was also associated with preeclampsia overall in age- and multivariable-adjusted models (Table 3). Results were unchanged when expanding the definition of preeclampsia to include ICD 10: O11 as no additional outcomes were identified in our study population.

Because missing data on smoking was significantly associated with preeclampsia, the primary analysis conservatively reclassified women with missing smoking data as smokers. Supplementary Table 1 shows how the association of interest was unchanged regardless of how missing smoking was handled.

Results were similar to the overall findings when we restricted to women without pregestational hypertension (Supplementary Table 2). There was insufficient power to examine the association among women with pregestational hypertension. Results were comparable when we extended the definition of pregestational hypertension to include a broader range of medications before LMP. This was true for both the adjusted RRs of the main effect, as well as the stratified analyses.

To investigate potential misclassification of lupus nephritis as early-onset preeclampsia, we excluded 36 pregnancies to women with possible pre-pregnancy renal disease or lupus nephritis in a sensitivity analysis. The association between SLE during pregnancy and early-

onset preeclampsia was similar to the primary analysis in age and multivariable-adjusted models where all identified SLE pregnancies were included.

Of the 6296 pregnancies in this population in the MBR from June 1, 2006 through end of 2012, 197 were among women with a history of APS as defined by ICD code D68.6 or heparin use during pregnancy. The majority of these (n=133, 68%) were among women with prevalent SLE during pregnancy. Due to limited statistical power, multivariable-adjusted models of early-onset preeclampsia were evaluated only in the context of all pregnancies. Adjustment for APS attenuated the association in early-onset preeclampsia for all pregnancies (RR 4.2, 95% CI 1.9, 9.1). The risk of our secondary outcome, any preeclampsia, was two-fold higher in SLE compared to the general population for first, subsequent, and all pregnancies and adjustment for APS did not appreciably alter the associations. (Supplementary table 3) When only relying on ICD-10 coding to define APS, there was little change in the association between SLE and our outcomes from the adjusted models summarized in table 3 (data not shown).

## Comment

Women with SLE during pregnancy have a substantially higher risk of preeclampsia before gestational week 34 compared to women from the general population. Despite an observed lower risk of this adverse pregnancy outcome in subsequent pregnancies likely due to a decreased likelihood of repeat pregnancies among women with a complicated first pregnancy, SLE remained a significant risk factor for early-onset preeclampsia in all and subsequent pregnancies. Sensitivity analyses showed that the association persisted after adjustment for APS and was probably not due to history of renal involvement. The impact of adjustment for APS was pronounced in early-onset preeclampsia whereas the attenuation was less pronounced when incorporating later preeclampsia. Pregestational hypertension is a known risk factor for preeclampsia, however, SLE was associated with early-onset preeclampsia in the absence of a history of hypertension.

We cannot exclude the possibility of misclassification of our outcome, preeclampsia, although previous validation studies have shown that this outcome in the MBR was reported with high accuracy.[12] Although we used the NPR to identify cases of preeclampsia, during the study period nearly all were also identified in the MBR. The NPR contained the date when preeclampsia was first observed in outpatient or inpatient care for the entire duration of our study. From 2001-2007 any stillbirth before 28 weeks were excluded, which may limit the suitability of the MBR for the analysis during this time. Restricting to 2008 onwards yielded comparable maternal age adjusted RR, although with very little power. Potential differential misclassification of preeclampsia in women with lupus nephritis because of its similarities with clinical features of lupus nephritis (e.g., proteinuria, hypertension), may overestimate the risk ratios. However, sensitivity analyses restricting to women with no nephrology care the year before pregnancy, yielded nearly identical results to those of the entire population. By excluding SLE patients with previous recent care by a nephrologist, a group known to have an increased likelihood of a preeclampsia diagnosis, we may have underestimated the risk of early-onset preeclampsia in all SLE patients in that sensitivity analysis.

In addition, we cannot exclude the possibility of residual confounding or misclassification of APS, although we defined APS as a combination of the ICD-10 code and heparin dispensing during pregnancy. This definition prohibits us from teasing apart the role of heparin during pregnancy from APS and data on specific serologic abnormalities such as lupus anticoagulant or other anti-phospholipid antibodies are not available. Our data had significant missing information on smoking, a factor that may be inversely associated with preeclampsia. This inverse association was not observed, which may be partly explained by the unequal distribution of missing information on self-reported first trimester smoking (15% missing among those with early-onset preeclampsia vs. 5% with no preeclampsia, Table 2). Therefore, we conducted sensitivity analyses using extreme values for the missing data and found that our results were essentially unchanged.

### Strengths of the study

Despite the potential limitations, the present study is one of the largest and the only one to assess the risk of early-onset preeclampsia in the setting of SLE, including 742 singleton births to mothers with preexisting SLE. Unfortunately, despite the large population-based nature of these data, power was limited to assess the role of risk factors exclusively in the pregnant SLE population, as others have been able to do for a variety of adverse pregnancy outcomes, including preeclampsia before 36 weeks gestation.[13] The increased risk, although partly explained by APS, persisted irrespective of APS status and even in the absence of pregestational hypertension, an important clinical risk factor for preeclampsia. Our data allowed for us to consider multiple definitions of important variables in this study. For example, our initial definition of hypertension incorporated medications with hypertension as the primary indication, which may have underestimated treated hypertension given that other therapies can be used. For that reason, we extended the definition of anti-hypertensives to include other agents such as calcium channel and beta blockers, which have multiple indications including hypertension, in a sensitivity analysis. The results were nearly identical. And lastly, we separated first from subsequent pregnancies, an important factor given that first pregnancy outcomes are generally worse than subsequent pregnancies, even in the general population.[14]

### Interpretation of the findings

This population-based approach yielded a contemporary unselected patient population from the entire country, which may more accurately represent the experience of all SLE patients in the population. Our data did not allow clinical phenotyping of SLE patients nor the assessment of disease activity, disease duration, or severity as some clinical cohorts have done. In cohort studies, quiescent SLE has been associated with uncomplicated pregnancies and increased disease activity associated with adverse pregnancy outcomes.[13] Unlike uncomplicated pregnancies more typical in the general population, women with SLE during pregnancy are more likely to receive additional maternal care from specialists in addition to midwives in Sweden. As a result, women with SLE may be surveilled more closely than those from the general population, which could influence when their preeclampsia was diagnosed. Given the standardized visit schedule with midwives, it is likely that preeclampsia is generally detected early in Sweden in both the general population and those with SLE.

The risk of early-onset preeclampsia in women with SLE may be due, at least in part, to the vasculopathic and antiangiogenic properties of IFNα, a cytokine implicated in the pathogenesis of SLE.[15] Although the etiology of preeclampsia is unknown, the trophoblast invasion and poor placentation are particularly important to the development of early-onset preeclampsia. Expression of vascular endothelial growth factor (VEGF) and placenta growth factor (PIGF) and their receptors on these invasive trophoblasts is important in normal placentation.[6] Additionally, these angiogenic factors are essential for health of maternal endothelium, particularly in the renal glomerulus.[16, 17] Elevated levels of IFNα create an anti-angiogenic and anti-proliferative milieu for the maternal endothelium.[15] Clinical and epidemiologic studies have found that endothelial cell dysfunction and related clinical syndromes and diseases, e.g., pregestational hypertension, also increase the risk of preeclampsia.

No studies, to date, have explicitly evaluated the risk of early-onset preeclampsia in SLE neither in the clinical environment nor using large administrative data or linkages. Using Nationwide Inpatient Sample data, Clowse and colleagues[2] reported an odds ratio of 3.0 for preeclampsia at any time during gestation and 4.4 for eclampsia in SLE exposed deliveries compared with non-SLE deliveries. Using British Columbia health care databases, Palmsten and colleagues[3] found a two-fold increased risk of preeclampsia associated with SLE. In a descriptive study of first singleton births in this population, we recently reported that 16% of the SLE exposed pregnancies had a preeclampsia diagnosis compared to just under 5% of those from the non-SLE general population comparator.[18] Other investigators have used a variety of data sources to examine composite adverse pregnancy outcomes in SLE patients, but not specifically early-onset preeclampsia and not always as the primary outcome.[13, 19] We found between a two- and three-fold increased risk of any preeclampsia in our analysis, which is consistent with previous studies of any preeclampsia in SLE pregnancy and clinical practice expectations.[20, 21]

## Conclusion

Not only are women with SLE at increased risk of preeclampsia before 34 weeks gestation, but this increased risk is not explained by pregestational hypertension or APS. Despite the relatively high frequency of commonly established risk factors of preeclampsia in SLE, they do not account for the entire risk of early-onset preeclampsia in this patient population when compared to the general population. Women with SLE during pregnancy should continue to be monitored carefully for early onset preeclampsia, particularly those with APS, and future research is needed to identify what factors within this population might be causing this serious adverse outcome.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

Maternal characteristics stratified by SLE status during pregnancy (prevalent vs. none) between Oct 21, 2001 and Dec 31, 2012 (presented as % unless otherwise specified).

| | **Prevalent SLE pregnancies** | | | **General Population pregnancies** | | |
|---|---|---|---|---|---|---|
| | ***First*** | ***Subsequent*** | ***All*** | ***First*** | ***Subsequent*** | ***All*** |
| | n=343 | n=399 | n=742 | n=4443 | n=6041 | n=10484 |
| Maternal age at delivery, mean (sd) | 30 (4.6) | 33 (4.5) | 32 (4.7) | 29 (4.8) | 33 (4.6) | 31 (4.9) |
| Maternal first trimester smoking | | | | | | |
| Yes | 3.5 | 7.3 | 5.5 | 7.0 | 7.8 | 7.5 |
| No | 90.4 | 87.5 | 88.5 | 88.1 | 87.0 | 87.7 |
| Missing | 6.1 | 4.8 | 5.9 | 4.9 | 5.8 | 4.8 |
| Obese (BMI ≥30 kg/m$^2$) | 8.8 | 9.3 | 9.0 | 8.4 | 11.5 | 10.2 |
| Maternal BMI missing | 11.4 | 9.8 | 10.5 | 10.4 | 10.3 | 10.3 |
| Pre-gestational hypertension | 5.8 | 4.3 | 5.0 | 0.2 | 0.2 | 0.2 |
| Pre-gestational diabetes | 2.0 | 3.5 | 2.8 | 0.6 | 1.8 | 1.3 |
| Anti-phospholipid syndrome * | 2.6 | 1.8 | 2.2 | 0 | 0 | 0 |

BMI=body mass index

* ICD10=D68.6 in Medical Birth Register and National Patient Register

## Table 2

Maternal characteristics by preeclampsia outcome for births between Oct 21, 2001 and Dec 31, 2012 (presented as % unless otherwise specified).

| | Preeclampsia | | |
|---|---|---|---|
| | **Any** | **Early (<34 weeks)** | **Normotensive** |
| | n=438 | n=87 | n=10788 |
| Age at delivery, mean (sd) | 30.9 (5.1) | 30.9 (5.5) | 31.3 (4.9) |
| First trimester smoking | | | |
| Yes | 4.6 | 6.9 | 7.4 |
| No | 87.4 | 78.2 | 87.8 |
| Missing | 8.0 | 14.9 | 4.8 |
| First trimester maternal BMI, median (IQR) | 25.6 (22.8, 29.9) | 25.8 (22.5, 29.4) | 23.5 (21.4, 26.4) |
| Obese (BMI ≥30 kg/m$^2$) | 21.9 | 19.5 | 9.6 |
| Maternal BMI missing | 12.3 | 17.2 | 10.3 |
| Pre-pregnancy hypertension | 1.8 | 3.5 | 0.5 |
| Pre-pregnancy diabetes | 3.2 | 2.3 | 1.3 |
| Anti-phospholipid syndrome ICD Code * | 0.1 | 1.2 | 0.5 |
| Systemic lupus erythematosus | 18.7 | 36.8 | 6.1 |

BMI=body mass index

* D68.6, in Medical Birth Register and National Patient Register

**Table 3**

Risk ratio of early-onset preeclampsia and all preeclampsia to women with SLE versus women from the general population in Sweden between October 2001 and December 2012

| | Early-onset preeclampsia <34 weeks | | | | All preeclampsia | | | |
|---|---|---|---|---|---|---|---|---|
| | Number | | Risk ratio (95% confidence interval) | | Number | | Risk ratio (95% confidence interval) | |
| Pregnancies | SLE | GP | Age-adjusted | Complete adjustment* | SLE | GP | Age-adjusted | Complete adjustment* |
| First | 24 | 34 | 9.4 (5.6, 15.6) | 9.3 (5.4, 16.3) | 56 | 225 | 3.2 (2.4, 4.2) | 3.2 (2.4, 4.2) |
| Subsequent | 8 | 21 | 5.2 (2.2, 12.5) | 4.7 (2.0, 11.2) | 26 | 131 | 2.9 (1.9, 4.4) | 2.6 (1.7, 4.2) |
| All | 32 | 55 | 8.1 (5.1, 12.9) | 7.8 (4.8, 12.9) | 82 | 356 | 3.2 (2.5, 4.1) | 3.1 (2.4, 4.0) |

SLE: systemic lupus erythematosus
GP: general population

*All multivariable adjusted models adjusted for maternal age, pregestational diabetes and hypertension, first-trimester smoking, and assuming all missing smokers are smokers (see Supplementary Table 1 for sensitivity analysis results)