# Pregnancy outcome predictors in systemic lupus erythematosus: a systematic review and meta-analysis

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# Pregnancy outcome predictors in systemic lupus erythematosus: a systematic review and meta-analysis

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## Summary

**Background** To enhance patient-tailored preconception risk assessment for women with systemic lupus erythematosus (SLE), knowledge on risk factors associated with adverse pregnancy outcomes is required. Therefore, we did a systematic review and meta-analysis to identify and provide unambiguous effect sizes of preconception predictors of pregnancy outcomes in women with SLE.

**Methods** In this systematic review and meta-analysis, we searched PubMed and Embase for studies reporting preconception predictors of pregnancy outcomes in women with SLE, from database inception to Aug 22, 2023. Studies were included if they presented original, quantitative data on pregnant women with SLE and reported on preconception risk factors on at least one of the outcomes as defined in the protocol. Studies were excluded if they had a sample size of less than 20 patients, were restricted to multiple pregnancies, had unclear timing of prognostication, or exclusively reported a composite outcome. Literature screening, data extraction, and risk-of-bias assessment (quality in prognostic studies tool) were done by two reviewers independently, in a blinded, standardised manner. The reported outcomes included livebirth, pre-eclampsia, small for gestational age, preterm birth, pregnancy loss before and after 20 weeks of gestation, and SLE flares. We computed pooled univariate odds ratios (ORs) and 95% CIs using a random effects model. We assessed heterogeneity using the $I^2$ statistic and prediction intervals. This study is registered with PROSPERO, CRD42022344732.

**Findings** Of the 6705 unique articles identified, 72 (1·1%) were included in the meta-analysis, comprising 10 355 pregnancies in 8065 women with SLE. One potentially eligible study was retracted and therefore removed from our analysis. Previous lupus nephritis was associated with decreased livebirth probability (OR 0·62 [95% CI 0·47–0·81]; $I^2$=0%), increased risk of preterm birth (2·00 [1·55–2·57]; $I^2$=17%), and increased risk of pre-eclampsia (3·11 [2·35–4·12]; $I^2$=0%). Chronic hypertension was associated with increased risk of disease flare (2·50 [1·74–3·58]; $I^2$=0%), preterm birth (2·65 [1·87–3·77]; $I^2$=0%), and pre-eclampsia (5·86 [3·41–10·06]; $I^2$=33%). SLE disease activity at conception or preconception was associated with increased risk of preterm birth (2·91 [1·96–4·33]; $I^2$=21%) and pre-eclampsia (2·32 [1·40–3·83]; $I^2$=0%). Secondary antiphospholipid syndrome was associated with decreased livebirth probability (0·40 [0·27–0·58]; $I^2$=0%), increased risk of pregnancy loss after 20 weeks of gestation (2·77 [1·44–5·31]; $I^2$=0%), and increased risk of preterm birth (1·65 [1·29–2·11]; $I^2$=0%). Across studies, risk-of-bias assessment suggested considerable bias in study attrition and confounding.

**Interpretation** We identified previous lupus nephritis, chronic hypertension, SLE disease activity before and at conception, and secondary antiphospholipid syndrome as predictors of adverse pregnancy outcomes in women with SLE. These findings contribute to an optimal patient-tailored risk assessment in preconception counselling.

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## Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by the presence of autoantibodies in combination with various signs and symptoms, such as rash, arthritis, anaemia, thrombocytopenia, serositis, nephritis, seizures, and psychosis.[1] SLE has an overall incidence of five per 100 000 people and is predominantly diagnosed in women of childbearing age.[1–3] Pregnancies in women with SLE impose an increased risk for disease flares. Additionally, patients with SLE are at increased risk of adverse pregnancy outcomes, particularly in the presence of risk factors such as active disease before or during conception or previous renal involvement.[4–6]

The most common pregnancy complications in women with SLE are pre-eclampsia, fetal growth restriction, preterm birth, disease flare, and fetal loss.[4–6] Furthermore, infants born to mothers with SLE who have anti-Sjögren's syndrome-related antigen A antibodies (anti-SSA) or anti-Sjögren's syndrome-related antigen B antibodies (SSB) have a 1–2% risk of developing congenital heart block associated with neonatal lupus.[7] Historically, these

## Research in context

### Evidence before this study

Pregnancies in women with systemic lupus erythematosus (SLE) carry an increased risk for disease flares and adverse pregnancy outcomes, particularly in the presence of certain risk factors. Therefore, multidisciplinary preconception counselling should be an integral part of managing patients with SLE. Although reviews on predictors of adverse pregnancy outcomes in patients with SLE have been done, a systematic review including a formal meta-analysis pooling effect sizes is missing in the literature. Importantly, study results vary and, consequently, the true effect size and robustness of predictors and their association with adverse outcomes remain uncertain. This systematic review and meta-analysis synthesised existing evidence to provide an unambiguous pooled effect estimate per preconception predictor related to pregnancy and disease outcomes. The search in PubMed and Embase included studies published from database inception until Aug 22, 2023, without language restrictions, and consisted of three main components: SLE, prediction studies, and pregnancy outcomes. Search terms included "systemic lupus erythematosus", "SLE", "validat*", "predict*", "model", "factor", "pregnancy", "preeclampsia", "birth", "labour", and "newborn".

### Added value of this study

We identified chronic hypertension, previous lupus nephritis, disease activity before and at conception, and secondary antiphospholipid syndrome as important predictors of adverse pregnancy outcomes and flares in women with SLE. The analyses report robust effect sizes for all the investigated predictors and outcomes, allowing for an improved preconception risk assessment for individual patients with SLE, prompting an optimisation of counselling before and during pregnancy for women with SLE.

### Implications of all the available evidence

The robust effect sizes for several predictors identified in this study can be incorporated into clinical guidelines for preconception counselling of women with SLE. These findings also provide essential background information for future studies creating prediction models for pregnancy outcomes.

potentially severe maternal and neonatal complications prompted health-care professionals to discourage pregnancy in women with SLE. Fortunately, advances in perinatal care, knowledge on treatment of SLE during pregnancy, and preconception counselling have substantially improved pregnancy outcomes.[8] Therefore, multidisciplinary preconception counselling should be an integral part of clinical management of patients with SLE of childbearing age.[9–11]

See Online for appendix 1

Preconception counselling should cover predictors for adverse pregnancy outcomes and disease flares to facilitate appropriate risk assessment, shared decision making, and tailored management plans before and during pregnancy.[9] Various predictors for adverse pregnancy outcomes in women with SLE have been identified, including disease activity within 6 months before conception, previous lupus nephritis, and secondary antiphospholipid syndrome.[12,13] However, because of high variation between individual studies, true effect sizes and robust predictors for adverse pregnancy outcomes remain uncertain.[4,12,14] Therefore, this study aims to address this evidence gap by aggregating all available evidence and provide a pooled effect estimate per preconception predictor related to pregnancy outcomes, contributing to an optimal, individual, preconception risk assessment for clinical use.

## Methods

### Search strategy and selection criteria

We did a systematic review and meta-analysis following PRISMA guidelines.[15] We searched PubMed and Embase for eligible articles published from database inception until Aug 22, 2023, without language restrictions. The search consisted of three main components: SLE, prediction studies, and pregnancy outcomes (full search strategy is given in appendix 1 p 1). We used the search filter used by Ingui and colleagues[16] to identify prediction studies.[17] To reduce publication bias, conference abstracts and short communications were also included.[18] To enhance the search, we searched reference lists of suitable articles for additional relevant publications.

Studies were included if they presented original, quantitative data on pregnant women with SLE and reported on preconception risk factors on at least one of the outcomes as defined in the protocol. The outcomes were livebirth, pre-eclampsia, small for gestational age, fetal growth restriction, birthweight, preterm birth, pregnancy loss before and after 20 weeks of gestation, gestational age, neonatal intensive care unit admission, fetal death, perinatal mortality, neonatal death, neonatal lupus, congenital heart block, antepartum or postpartum thrombosis, Apgar score, and SLE flares. SLE had to have been defined on the basis of the 2019 European League Against Rheumatism–American College of Rheumatology, the 2012 Systemic Lupus International Collaborating Clinics, or the 1997 American College of Rheumatology SLE classification criteria.[19–21] The timeframe for follow-up on the pregnancy outcomes was defined as the beginning of pregnancy until 6 weeks postpartum and for SLE flares until 12 months postpartum.

We excluded studies that had a sample size of fewer than 20 patients in compliance with previous reviews,[22,23] reported on patient populations restricted to multiple pregnancies, solely used predictors that are unknown at time of preconception counselling (eg, laboratory

parameters measured in the first trimester of pregnancy), or exclusively reported on a composite outcome without information on the individual outcome components. Corresponding authors were contacted if important data were missing, definitions or timing of prognostication were unclear, or if only composite outcomes were reported. Preconception treatment effects on pregnancy outcome prediction were beyond the scope of this review.

Two authors (MW and JF) independently screened for study eligibility (title and abstract screening and full-text screening), extracted data, and assessed risk of bias in a blinded, standardised manner. Following each phase, masking was suspended, and any discrepancies were addressed through discussion and resolution involving an independent third author (JK). For eligible duplicate studies, we included those with the most complete data on predictors and outcomes of interest. Data extraction was based on the CHARMS-PF checklist; a modified version of the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS).[24,25] The classification of study design (prospective or retrospective) of the included articles was based on the methodology used for patient enrolment, as described by the authors in the original publication. For categorical predictors, univariate odds ratios (ORs) were extracted. If ORs were not available or reported, event rates were extracted. We did the risk-of-bias assessment of included studies using the quality in prognostic studies (QUIPS) tool.[26]

The protocol for this systematic review and meta-analysis was registered with PROSPERO, CRD42022344732.

## Data analysis

Data were included in the meta-analysis if at least two studies independently reported the OR or a contingency table of the same predictor and outcome. Definitions of predictors and outcomes in the pooled analyses are presented in appendix 2. We calculated summary estimates by random-effects meta-analysis using the generic inverse variance method and the Paule–Mandel estimator to identify the random-effects weights.[27]

We characterised between-study heterogeneity using the $I^2$ statistic (0–100%). Because an $I^2$ of 75% or greater represents considerable heterogeneity according to the Cochrane handbook, effect sizes were exclusively pooled if $I^2$ was below 75%.[28] To study possible causes of between-study heterogeneity, we planned subgroup analyses for different SLE diagnostic criteria and SLE with or without secondary antiphospholipid syndrome. If at least ten studies were included in a meta-analysis, publication bias was assessed by visual inspection of a funnel plot, and by use of Egger's test.[28,29]

Robustness of the associations between predictors and pregnancy outcomes was further studied through the calculation of 95% prediction intervals of the pooled effect sizes.[30] Prediction intervals were based on both the between-study heterogeneity variance and the SE of the pooled effect. Prediction intervals establish a range within which we can anticipate the potential effects of future studies. If the regular 95% CI implies statistical significance, but the 95% prediction interval of the pooled OR crosses 1, the finding introduces an element of uncertainty regarding the prospective association between the predictor and the outcome, provided future studies are done within a similar context. Conversely, if statistical significance of a pooled effect estimate is supported by its 95% prediction interval, the result underscores the robustness of the found effect. It is important to note that wide prediction intervals are common.[31]

In August, 2023, we made an amendment to the protocol for additional sensitivity analyses. For outcomes with considerable heterogeneity of $I^2$ between 50% and 75%, between-study heterogeneity was further explored by basic outlier removal and influence analysis, including a Baujat plot and a leave-one-out analysis. All analyses were done using R (version 4.2.1), with packages "dmetar", "meta", and "forestplot".[31–33]

## Role of the funding source

There was no funding source for this study.

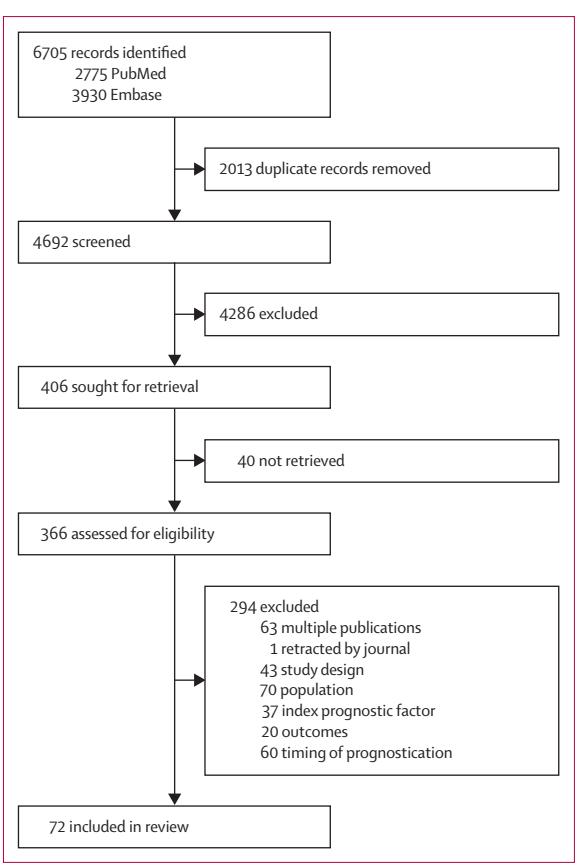


*Figure 1:* **Study selection**

See **Online** for appendix 2

| | Study design | Location | Participants | Enrolment period | Pooled predictors | Pooled Outcomes |
|---|---|---|---|---|---|---|
| Al-Riyami et al (2021)[34] | Retrospective | Oman | 149 SLE pregnancies (98 women) | August, 2006–October, 2016 | Antiphospholipid syndrome, anticardiolipin antibodies, chronic hypertension, anti-SSA, and anti-SSB | Livebirth, pregnancy loss >20 weeks, pre-eclampsia, preterm birth, and flare |
| Attia et al (2019)[35] | Prospective | Egypt | 119 SLE pregnancies (73 women) | January, 2006–December, 2017 | Previous lupus nephritis and active SLE at conception | Livebirth, neonatal mortality, pregnancy loss >20 weeks, early pregnancy loss, small for gestational age, low birthweight, pre-eclampsia, preterm birth, and flare |
| Borella et al (2014)[36] | Prospective | Italy | 132 SLE pregnancies (96 women) | 1990–2008 | NA* | NA |
| Bramham et al (2011)[37] | Retrospective | England | 107 SLE pregnancies (83 women) | January, 2000–October, 2008 | Previous lupus nephritis | Livebirth, pregnancy loss >20 weeks, small for gestational age, Apgar score, pre-eclampsia, preterm birth, and flare |
| Brucato et al (2002)[38] | Prospective | Italy | 147 SLE pregnancies (111 women) | Unclear | Anti-SSA | Livebirth, early pregnancy loss, preterm birth, and flare |
| Buyon et al (2017)[39] | Prospective | USA, Canada | 373 SLE pregnancies (373 women) | September, 2003–December, 2012 | Nulliparity | Flare |
| Carmona et al (2005)[40] | Retrospective | Spain | 108 SLE pregnancies (99 women) | January, 1995–December, 2001 | Previous lupus nephritis | Livebirth, early pregnancy loss, pre-eclampsia, preterm birth, and flare |
| Ceccarelli et al (2021)[41] | Prospective | Italy | 70 SLE pregnancies (50 women) | 2008–unknown | Anti-SSA | Flare |
| Chakravarty et al (2005)[42] | Retrospective | USA | 63 SLE pregnancies (48 women) | 1991–2001 | NA* | NA |
| Chen et al (2015)[43] | Retrospective | China | 64 SLE pregnancies (62 women) | January, 2008–December, 2013 | Active SLE at conception | Livebirth, pregnancy loss >20 weeks, pre-eclampsia, preterm birth, and flare |
| Chen et al (2022)[44] | Retrospective | China | 158 SLE pregnancies (155 women) | January, 2010–December, 2016 | Active SLE at conception | Livebirth, neonatal mortality, small for gestational age, low birthweight, preterm birth, and flare |
| Crisafulli et al (2023)[45] | Retrospective | Italy | 246 SLE pregnancies (172 women) | 1987–2018 | Antiphospholipid syndrome, anti-SSA, anti-dsDNA, low C3, and low C4 | Pre-eclampsia and flare |
| Davis-Porada et al (2020)[46] | Prospective | USA, Canada | 384 SLE pregnancies (384 women) | September, 2003–December, 2012 | Previous lupus nephritis | Flare |
| De la Hera Madrazo et al (2022)[47] | Retrospective | Spain | 64 SLE pregnancies (37 women) | January, 2005–April, 2019 | NA* | NA |
| Deguchi et al (2018)[48] | Prospective | Japan | 56 SLE pregnancies (46 women) | April, 2009–March, 2016 | Previous lupus nephritis, active SLE at conception, and antiphospholipid syndrome | Livebirth, small for gestational age, pre-eclampsia, and preterm birth |
| Eudy et al (2019)[49] | Prospective | USA | 309 SLE pregnancies (261 women) | 1987–2015 | NA* | NA |
| Fatemi et al (2013)[50] | Retrospective | Iran | 72 SLE pregnancies (65 women) | 1998–2012 | Previous lupus nephritis and anti-SSA | Pregnancy loss >20 weeks, pre-eclampsia, and flare |
| Foocharoen et al (2009)[51] | Retrospective | Thailand | 37 SLE pregnancies (37 women) | January, 1997–December, 2006 | Active SLE at conception | Livebirth, pregnancy loss >20 weeks, and small for gestational age |
| Gaballa et al (2012)[52] | Unclear | Egypt | 40 SLE pregnancies (40 women) | March, 2008–October, 2010 | Active SLE at conception | Flare |
| Hiramatsu et al (2021)[53] | Retrospective | Japan | 108 SLE pregnancies (74 women) | January, 2000–October, 2020 | Active SLE at conception, antiphospholipid syndrome, antiphospholipid antibodies, chronic hypertension, anti-SSA, anti-Smith antibodies, anti-ribonucleoprotein antibodies, and anti-dsDNA | Preterm birth |
| Hussein Aly et al (2016)[54] | Prospective | Egypt | 91 SLE pregnancies (84 women) | October, 2010–January, 2015 | Previous lupus nephritis, chronic hypertension, and antiphospholipid syndrome | Pregnancy loss >20 weeks, neonatal mortality, small for gestational age, low birthweight, preterm birth, and flare |
| Hwang et al (2018)[55] | Prospective | South Korea | 92 SLE pregnancies (77 women) | June, 2007–June, 2013 | Anti-SSA, anti-SSB, anticardiolipin antibodies, lupus anticoagulant, B2GP1, anti-Smith antibodies, and anti-dsDNA | Flare |

(Table continues on next page)

| | Study design | Location | Participants | Enrolment period | Pooled predictors | Pooled Outcomes |
|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | |
| Ignacchiti Lacerda et al (2021)[56] | Retrospective | Brazil | 151 SLE pregnancies (139 women) | January, 2011–December, 2016 | Previous lupus nephritis, active SLE at conception, antiphospholipid syndrome, antiphospholipid antibodies, anti-SSA, anti-SSB, anti-Smith antibodies, and anti-ribonucleoprotein antibodies | Small for gestational age |
| Imbasciati et al (2009)[57] | Retrospective | Italy | 113 SLE pregnancies (81 women) | 1985–2004 | NA* | NA |
| Irino et al (2021)[58] | Retrospective | Japan | 64 SLE pregnancies (39 women) | October, 2002–May, 2018 | Previous lupus nephritis, active SLE at conception, antiphospholipid syndrome, antiphospholipid antibodies, anti-SSA, and anti-dsDNA | Livebirth, preterm birth, and flare |
| Janardana et al (2020)[59] | Retrospective | India | 121 SLE pregnancies (80 women) | 2013–18 | Active SLE at conception | Flare |
| Jiang et al (2020)[60] | Retrospective | China | 513 SLE pregnancies (484 women) | November, 2010–December, 2018 | Active SLE at conception and chronic hypertension | Pre-eclampsia |
| Kalok et al (2019)[61] | Retrospective | Malaysia | 71 SLE pregnancies (44 women) | January, 2007–December, 2014 | Previous lupus nephritis, active SLE at conception, and antiphospholipid syndrome | Small for gestational age, pre-eclampsia, preterm birth, and flare |
| Ko et al (2011)[62] | Retrospective | South Korea | 183 SLE pregnancies (143 women) | January, 1998–December, 2010 | Previous lupus nephritis, active SLE at conception, and antiphospholipid antibodies | Livebirth, neonatal mortality, Pregnancy loss >20 weeks, Apgar score, small for gestational age, low birthweight, and preterm birth |
| Koh et al (2015)[63] | Retrospective | South Korea | 179 SLE pregnancies (128 women) | January, 1998–December, 2012 | Previous lupus nephritis | Livebirth, neonatal mortality, Apgar score, small for gestational age, pre-eclampsia, and preterm birth |
| Koh et al (2015)[64] | Retrospective | South Korea | 183 SLE pregnancies (132 women) | January, 1998–December, 2012 | Previous lupus nephritis, active SLE at conception, antiphospholipid syndrome, anticardiolipin antibodies, lupus anticoagulant, B2GP1, anti-SSA, anti-SSB, anti-Smith antibodies, anti-ribonucleoprotein antibodies, and anti-dsDNA | Flare |
| Kroese et al (2017)[65] | Retrospective | Netherlands | 144 SLE pregnancies (96 women) | 2000–15 | Antiphospholipid syndrome and antiphospholipid antibodies | Pregnancy loss >20 weeks, small for gestational age, pre-eclampsia, preterm birth, and flare |
| Lacerda et al (2021)[66] | Retrospective | Brazil | 260 SLE pregnancies (260 women) | 2011–20 | NA* | NA |
| Lao et al (2023)[67] | Retrospective | China | 280 SLE pregnancies | January, 2013–October, 2022 | NA* | NA |
| Larosa et al (2022)[68] | Prospective | France | 238 SLE pregnancies (238 women) | October, 2014–July, 2019 | Antiphospholipid syndrome | Flare |
| Li et al (2022)[69] | Retrospective | China | 167 SLE pregnancies (150 women) | January, 2010–January, 2020 | Active SLE at conception | Flare |
| Louthrenoo et al (2021)[70] | Retrospective | Thailand | 90 SLE pregnancies (77 women) | January, 1993–June, 2017 | Active SLE at conception, chronic hypertension, and antiphospholipid antibodies | Livebirth, small for gestational age, low birthweight, preterm birth, and flare |
| Madazli et al (2014)[71] | Retrospective | Turkey | 65 SLE pregnancies (65 women) | January, 2002–February, 2011 | Antiphospholipid syndrome and antiphospholipid antibodies | Pregnancy loss >20 weeks and preterm birth |
| Maeda et al (2021)[72] | Retrospective | Japan | 76 SLE pregnancies (76 women) | January, 2002–December, 2017 | Previous lupus nephritis, antiphospholipid syndrome, and chronic hypertension | Pre-eclampsia |
| Mecacci et al (2009)[73] | Retrospective | Italy | 62 SLE pregnancies (58 women) | January, 1998–June, 2006 | Antiphospholipid syndrome and antiphospholipid antibodies | Livebirth, early pregnancy loss, preterm birth, and flare |
| Mecacci et al (2019)[74] | Retrospective | Italy | 99 SLE pregnancies (88 women) | 2007–15 | Previous lupus nephritis and antiphospholipid antibodies | Livebirth, Apgar score, small for gestational age, pre-eclampsia, and flare |

(Table continues on next page)

| | Study design | Location | Participants | Enrolment period | Pooled predictors | Pooled Outcomes |
|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | |
| Miranda-Hernandez et al (2021)[75] | Prospective | Mexico | 351 SLE pregnancies (317 women) | January, 2009–December, 2018 | Previous lupus nephritis, active SLE at conception, antiphospholipid syndrome, antiphospholipid antibodies, chronic hypertension, anti-SSA, and anti-SSB | Live irth, neonatal mortality, low birthweight, pregnancy loss >20 weeks, and preterm birth |
| Mokbel et al (2023)[76] | Prospective | Egypt | 201 SLE pregnancies (123 women) | January, 2007–December, 2021 | Active SLE at conception, antiphospholipid syndrome, chronic hypertension, and nulliparity | Pre-eclampsia, preterm birth, and flare |
| Moroni et al (2016)[77] | Prospective | Italy | 71 SLE pregnancies (61 women) | October, 2006–December, 2013 | NA* | NA |
| Moroni et al (2016)[78] | Prospective | Italy | 71 SLE pregnancies (61 women) | October, 2006–December, 2013 | NA* | NA |
| Moroni et al (2002)[79] | Retrospective | Italy | 51 SLE pregnancies (38 women) | June, 1968–February, 2000 | NA* | NA |
| Murata et al (2022)[80] | Retrospective | Japan | 52 SLE pregnancies (52 women) | January, 2006–March, 2020 | Previous lupus nephritis, antiphospholipid syndrome, anti-SSA, and anti-SSB | Small for gestational age, low birthweight, pre-eclampsia, and preterm birth |
| Nakai et al (2021)[81] | Retrospective | Japan | 34 SLE pregnancies (32 women) | April, 2003–December, 2020 | NA* | NA |
| Ntali et al (2022)[82] | Prospective | Greece | 82 SLE pregnancies (64 women) | January, 2015–January, 2018 | Previous lupus nephritis, anticardiolipin antibodies, B2GP1, anti-SSA, anti-SSB, anti-Smith antibodies, and anti-dsDNA | Early pregnancy loss, small for gestational age, preterm birth, and flare |
| Oishi et al (2021)[83] | Retrospective | Japan | 98 SLE pregnancies (57 women) | January, 1996–March, 2018 | Previous lupus nephritis, antiphospholipid syndrome, antiphospholipid antibodies, and chronic hypertension | Livebirth, pregnancy loss >20 weeks, low birthweight, pre-eclampsia, preterm birth, and flare |
| Ong et al (2021)[84] | Retrospective | Malaysia | 131 SLE pregnancies (93 women) | January, 2008–May, 2020 | Previous lupus nephritis, active SLE at conception, antiphospholipid syndrome, lupus anticoagulant, anticardiolipin antibodies, B2GP1, chronic hypertension, anti-SSA, anti-SSB, anti-Smith antibodies, anti-ribonucleoprotein antibodies, anti-dsDNA, low C3, and low C4 | Livebirth, pregnancy loss >20 weeks, small for gestational age, pre-eclampsia, preterm birth, and flare |
| Otaduy et al (2021)[85] | Retrospective | Argentina | 121 SLE pregnancies (77 women) | January, 2015–April, 2017 | Previous lupus nephritis and anti-SSA | Livebirth, early pregnancy loss, pregnancy loss >20 weeks, low birthweight, pre-eclampsia, preterm birth, and flare |
| Park et al (2014)[86] | Retrospective | South Korea | 62 SLE pregnancies (50 women) | November, 1994–December, 2010 | Previous lupus nephritis, antiphospholipid antibodies, anticardiolipin antibodies, lupus anticoagulant, and nulliparity | Flare |
| Pastore et al (2019)[87] | Retrospective | Brazil | 102 SLE pregnancies (95 women) | January, 2012–January, 2018 | Active SLE at conception | Preterm birth and Apgar score |
| Poh et al (2020)[88] | Retrospective | Singapore | 75 SLE pregnancies (45 women) | 2000–16 | Previous lupus nephritis and antiphospholipid syndrome | Livebirth, early pregnancy loss, neonatal mortality, Apgar score, small for gestational age, pre-eclampsia, preterm birth, and flare |
| Rodrigues et al (2019)[89] | Retrospective | Brazil | 147 SLE pregnancies (137 women) | January, 2011–December, 2016 | Previous lupus nephritis | Pregnancy loss >20 weeks, pre-eclampsia, and flare |
| Saavedra et al (2020)[90] | Prospective | Mexico | 317 SLE pregnancies (316 women) | January, 2009–December, 2018 | Previous lupus nephritis, active SLE at conception, and antiphospholipid syndrome | Pre-eclampsia |
| Saavedra et al (2016)[91] | Retrospective | Mexico | 186 SLE pregnancies (180 women) | January, 2005–August, 2013 | NA* | NA |
| Saavedra et al (2012)[92] | Retrospective | Mexico | 95 SLE pregnancies (92 women) | January, 2005–December, 2009 | Previous lupus nephritis and anti-SSA | Livebirth, neonatal mortality, pregnancy loss >20 weeks, early pregnancy loss, low birthweight, pre-eclampsia, preterm birth, and flare |
| Saavedra et al (2015)[93] | Retrospective | Mexico | 124 SLE pregnancies (120 women) | January, 2005–June, 2011 | Previous lupus nephritis | Pre-eclampsia and flare |

(Table continues on next page)

| | Study design | Location | Participants | Enrolment period | Pooled predictors | Pooled Outcomes |
|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | |
| Saleh et al (2020)[94] | Prospective | Sweden | 59 SLE pregnancies (28 women) | 2002–18 | Previous lupus nephritis, antiphospholipid syndrome, antiphospholipid antibodies, lupus anticoagulant, B2GP1, anti-SSA, anti-SSB, low C3, and low C4 | Early pregnancy loss, small for gestational age, pre-eclampsia, and preterm birth |
| Seo et al (2019)[95] | Retrospective | South Korea | 151 SLE pregnancies (122 women) | December, 1995–April, 2018 | Anti-SSA and anti-SSB | Pre-eclampsia |
| Shaharir et al (2020)[96] | Retrospective | Malaysia | 240 SLE pregnancies (153 women) | January, 2016–December, 2019 | Chronic hypertension | Pre-eclampsia |
| Shaharir et al (2019)[97] | Retrospective | Malaysia | 192 SLE pregnancies (120 women) | January, 2016–December, 2018 | Previous lupus nephritis, active SLE at conception, and antiphospholipid syndrome | Flare |
| Shu et al (2020)[98] | Unclear | China | 82 SLE pregnancies (78 women) | February, 2012–January, 2017 | Active SLE at conception, antiphospholipid syndrome, anticardiolipin, and anti-dsDNA | Livebirth and flare |
| Tani et al (2021)[99] | Retrospective | Italy, Germany | 347 SLE pregnancies (281 women) | 1995–2018 | Antiphospholipid syndrome, chronic hypertension, antiphospholipid antibodies, anticardiolipin antibodies, lupus anticoagulant, anti-SSA, anti-SSB, and anti-dsDNA | Livebirth, pregnancy loss >20 weeks, small for gestational age, pre-eclampsia, preterm birth, and flare |
| Tedeschi et al (2015)[100] | Retrospective | USA | 147 SLE pregnancies (113 women) | 1990–2013 | Active SLE at conception, previous lupus nephritis, antiphospholipid syndrome, anticardiolipin antibodies, lupus anticoagulant, anti-SSA, anti-SSB, and anti-dsDNA | Flare |
| Teh et al (2017)[101] | Retrospective | Malaysia | 115 SLE pregnancies (86 women) | January, 2006–December, 2015 | Active SLE at conception | Flare |
| Ueda et al (2020)[102] | Retrospective | Japan | 54 SLE pregnancies (54 women) | January, 2005–December, 2019 | Anti-SSA, anti-SSB, anti-dsDNA, low C3, low C4, and nulliparity | Flare |
| Wagner et al (2009)[103] | Retrospective | USA | 90 SLE pregnancies (58 women) | 1976–August, 2007 | Previous lupus nephritis | Livebirth, small for gestational age, and preterm birth |
| Wu et al (2019)[104] | Retrospective | China | 338 SLE pregnancies (women unclear) | September, 2011–May, 2017 | Chronic hypertension and anti-SSB | Livebirth |
| Zamani et al (2020)[105] | Retrospective | Iran | 121 SLE pregnancies (59 women) | 2003–17 | Antiphospholipid syndrome | Pregnancy loss >20 weeks, preterm birth, and low birthweight |

Given the extensive number of included studies we exclusively reported the pooled predictors and pooled outcomes for which we were able to pool odds ratios. B2GP1=anti-β2-glycoprotein 1. dsDNA=double-stranded DNA. NA=not applicable. SLE=systemic lupus erythematosus. *For some studies, no odds ratios could be pooled.

***Table:*** **Characteristics of included studies**

## Results

The search identified 6705 records (figure 1). After removal of 2013 (30%) duplicate records, 4692 (70%) unique records were screened by title and abstract. Of those, 4286 (91%) were excluded on the basis of eligibility criteria. The hierarchy of reasons of exclusion and the list of studies excluded at full-text screening stage are given in appendix 1 (pp 2–9). Of the 366 full-text records that were assessed for eligibility, 72 (20%) were included in the review and meta-analysis (table).

Of the 92 pooled ORs, 80 (87%) had an $I^2$ of less than 50%. Detailed forest plots of each meta-analysis with study-specific effect sizes and weights including prediction intervals are given in appendix 1 (p 10–26). We found no significant prediction intervals for the outcomes low birthweight, Apgar score, and neonatal mortality (appendix 1 pp 24–26). Given the large number of included studies, here we describe analysis outcomes with at least one predictor that showed an $I^2$ less than 75%, with both a significant CI and prediction interval, as these results provide the most robust findings. Results of the full analyses are in appendix 1 (p 10–26).

For the outcome livebirth (figure 2), the following potential predictors were identified in 25 studies: previous lupus nephritis, active SLE before or during conception, secondary antiphospholipid syndrome, chronic hypertension, anti-SSA, anti-SSB, anticardiolipin antibodies, and anti-double-stranded DNA (anti-dsDNA) positivity.[34,35,37,38,40,43,44,48,51,58,62,64,70,73–75,83–85,88,92,98,99,103,104]

Previous lupus nephritis (OR 0·62 [95% CI 0·47–0·81]; $I^2$=0%) and secondary antiphospholipid syndrome (0·40 [0·27–0·58]; $I^2$=0%) were associated with a decreased livebirth probability. Active SLE before and during conception showed a significant decreased livebirth probability, although we found uncertainty in the prediction interval (0·34 [0·19–0·62]; $I^2$=52%; appendix 1 p 10). Chronic hypertension, anti-SSA, anti-SSB,

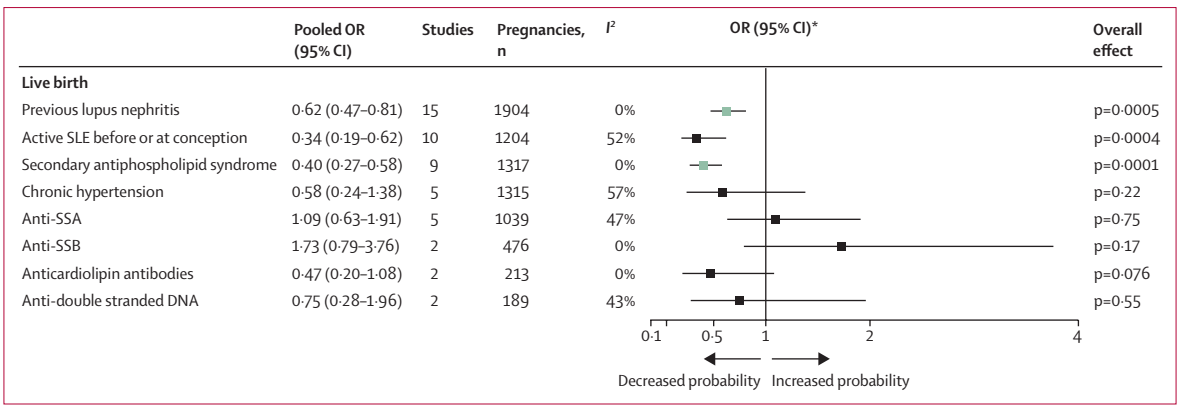


***Figure 2*: Summary of meta-analyses for the outcome livebirth**
ORs with both a significant 95% CI and prediction interval are highlighted in green. Anti-SSA=anti-Sjögren's syndrome-related antigen A antibodies. Anti-SSB=anti-Sjögren's syndrome-related antigen B antibodies. OR=odds ratio. SLE=systemic lupus erythematosus. *Inverse variance, random effects.

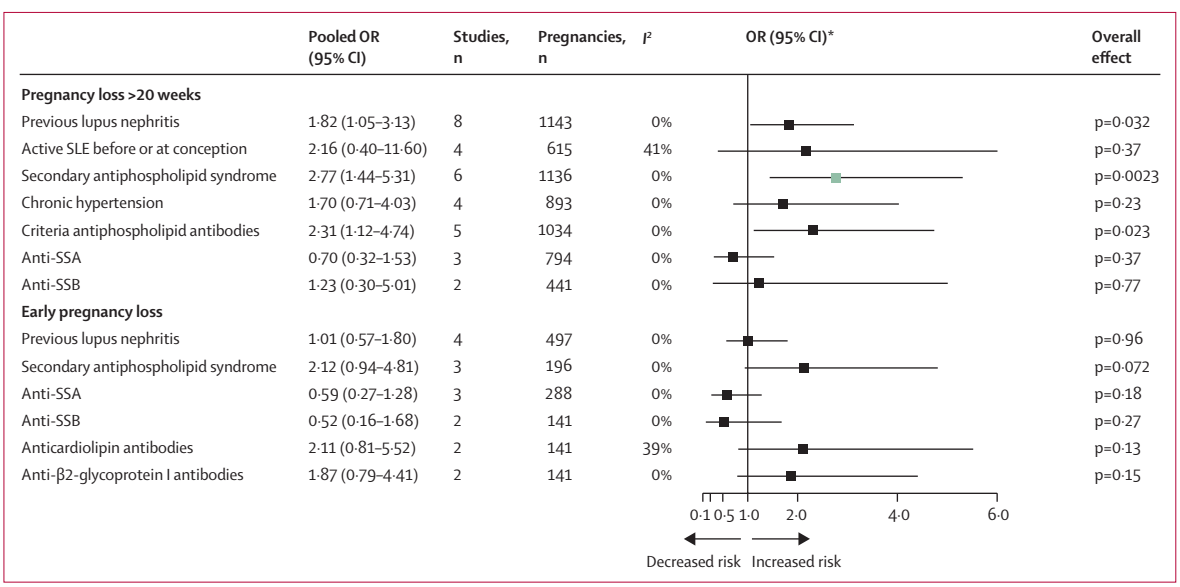


***Figure 3*: Predictors of the outcome pregnancy loss**
ORs with both a significant 95% CI and prediction interval are highlighted in green. Anti-SSA=anti-Sjögren's syndrome-related antigen A antibodies. Anti-SSB=anti-Sjögren's syndrome-related antigen B antibodies. OR=odds ratio. SLE=systemic lupus erythematosus. *Inverse variance, random effects.

anticardiolipin antibodies, and anti-dsDNA positivity were not significantly associated with the outcome livebirth (figure 2).

For pregnancy loss, spanning all trimesters, we studied the following predictors in 23 studies: previous lupus nephritis, active SLE before or during conception, secondary antiphospholipid syndrome, chronic hypertension, criteria antiphospholipid antibodies, anti-SSA, anti-SSB, anticardiolipin antibodies, and anti-β2-glycoprotein 1 antibody (a β2GP1) positivity (figure 3).[34,35,37,38,40,43,50,51,54,62,65,71,73,75,82,83,85,88,89,92,94,99,105] Secondary antiphospholipid syndrome showed a significant association (OR 2·77 [95% CI 1·44–5·31]; $I^2$=0%) and prediction interval with pregnancy loss after 20 weeks of gestation (figure 3; appendix 1 p 12). We also found statistically significant associations but without significant prediction intervals between previous lupus nephritis and criteria antiphospholipid antibodies with pregnancy loss after 20 weeks of gestation (appendix 1 pp 11–12).

The definitions of pregnancy loss varied considerably across studies and none of the studied predictors were found to be significantly associated with early pregnancy loss (before 20 weeks of gestation; figure 3).

32 studies reported on risk factors for preterm birth, including previous lupus nephritis, active SLE before or during conception, secondary antiphospholipid syndrome, chronic hypertension, low C3, low C4, criteria antiphospholipid antibodies, anti-SSA, anti-SSB, anticardiolipin antibodies, lupus anticoagulant, aß2GP1, anti-dsDNA, anti-Smith antibodies, and anti-ribonucleoprotein antibody positivity (figure 4).[34,35,37,38,40,43,44,48,53,54,58,61,62,64,65,70,71,73,75,76,80,82–85,87,88,92,94,99,103,105]

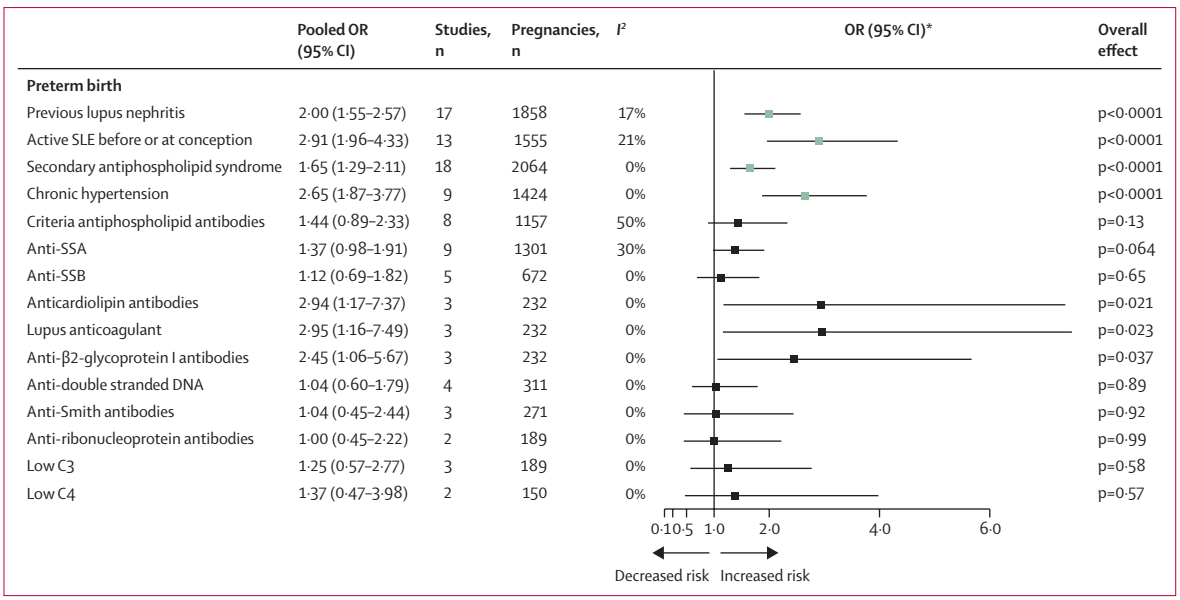


***Figure 4*: Predictors of the outcome preterm birth**
ORs with both a significant 95% CI and prediction interval are highlighted in green. Anti-SSA=anti-Sjögren's syndrome-related antigen A antibodies. Anti-SSB=anti-Sjögren's syndrome-related antigen B antibodies. OR=odds ratio. SLE=systemic lupus erythematosus. *Inverse variance, random effects.

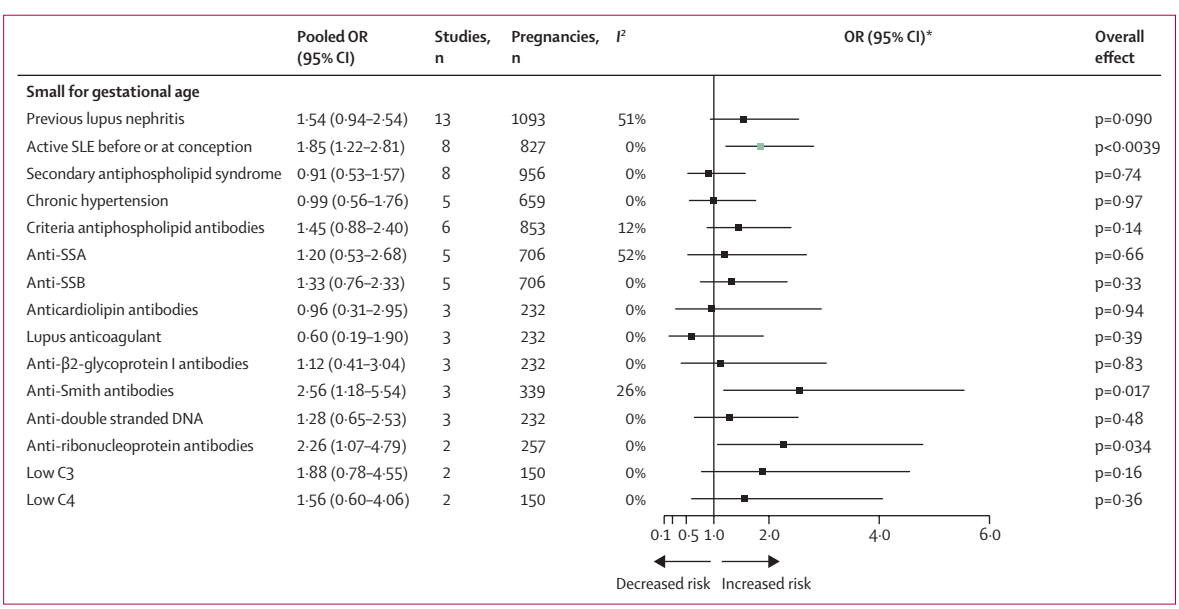


***Figure 5*: Predictors of the outcome small for gestational age**
ORs with both a significant 95% CI and prediction interval are highlighted in green. Anti-SSA=anti-Sjögren's syndrome-related antigen A antibodies. Anti-SSB=anti-Sjögren's syndrome-related antigen B antibodies. OR=odds ratio. SLE=systemic lupus erythematosus. *Inverse variance, random effects.

Preterm birth was defined as livebirth before 37 weeks of gestation in 31 (97%) of 32 studies. Women with previous lupus nephritis (OR 2·00 [95% CI 1·55–2·57]; $I^2$=17%), active SLE before or during conception (2·91 [1·96–4·33]; $I^2$=21%), secondary antiphospholipid syndrome (1·65 [1·29–2·11]; $I^2$=0%), and chronic hypertension (2·65 [1·87–3·77; $I^2$=0%) were at increased risk of preterm birth (figure 4). Positivity of separate antiphospholipid antibodies (anticardiolipin, lupus anticoagulant, and aβ2GP1) showed a statistically significant association with preterm birth, but without significant prediction intervals (figure 4; appendix 1 pp 13–15).

In 17 (85%) of 20 studies studying predictors for fetal growth restriction or small for gestational age, a consistent definition and differentiation between both outcomes was absent (figure 5). Consequently, we decided to combine all

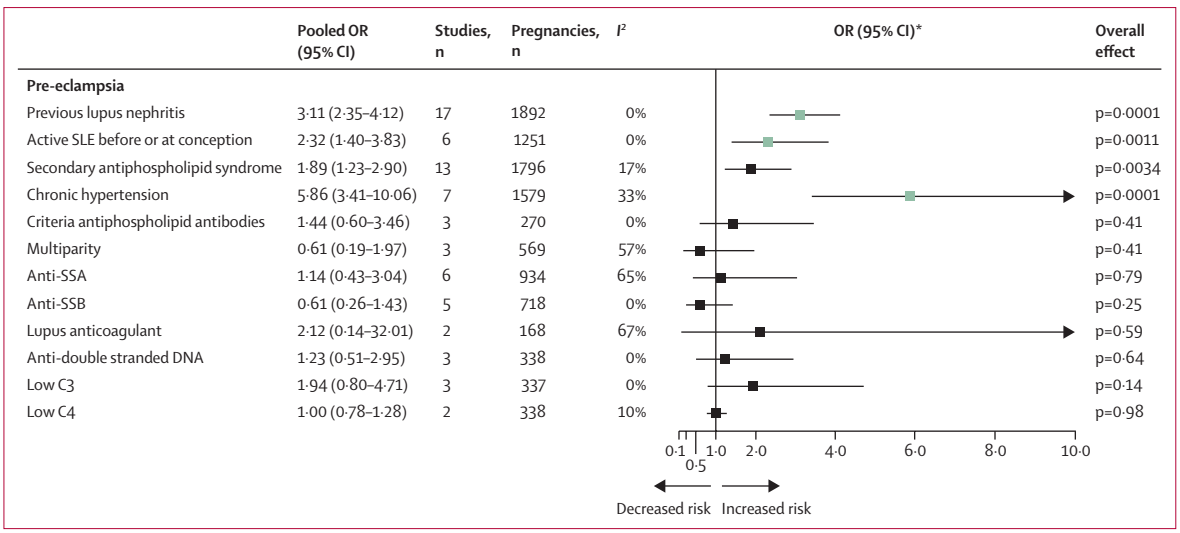


***Figure 6*: Predictors of the outcome pre-eclampsia**

ORs with both a significant 95% CI and prediction interval are highlighted in green. Anti-SSA=anti-Sjögren's syndrome-related antigen A antibodies. Anti-SSB=anti-Sjögren's syndrome-related antigen B antibodies. OR=odds ratio. SLE=systemic lupus erythematosus. *Inverse variance, random effects.

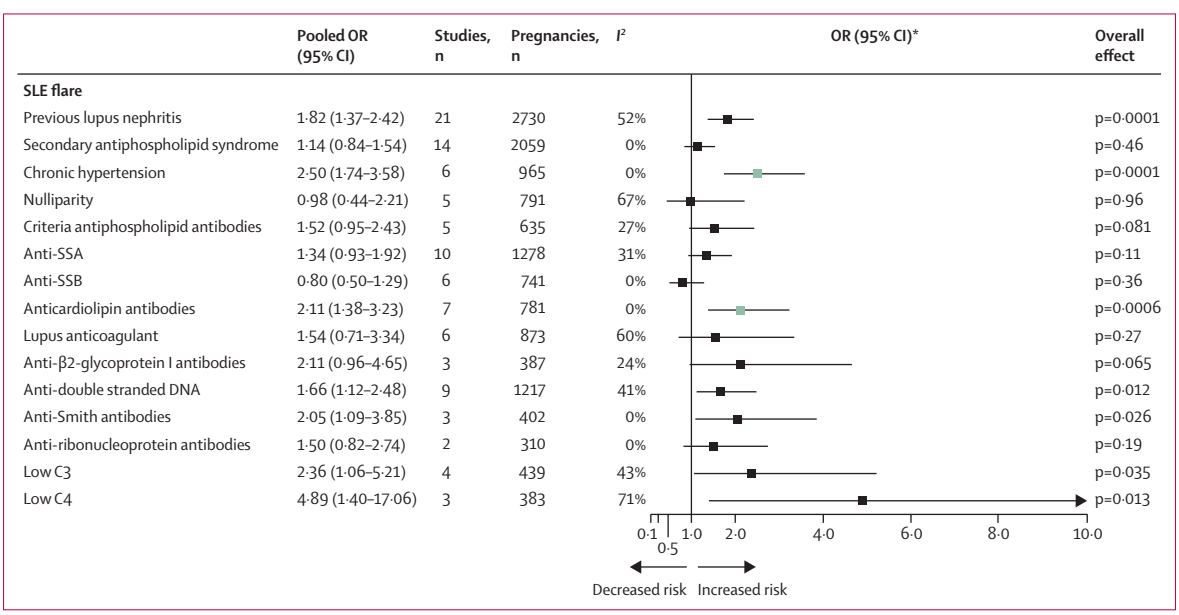


***Figure 7*: Predictors of the outcome SLE flare**

ORs with both a significant 95% CI and prediction interval are highlighted in green. Anti-SSA=anti-Sjögren's syndrome-related antigen A antibodies. Anti-SSB=anti-Sjögren's syndrome-related antigen B antibodies. OR=odds ratio. SLE=systemic lupus erythematosus. *Inverse variance, random effects.

studies that examined either small for gestational age or fetal growth restriction because they all complied with the definition of an estimated fetal weight below the 10th percentile. Previous lupus nephritis, active SLE before or during conception, secondary antiphospholipid syndrome, chronic hypertension, low C3, low C4, criteria antiphospholipid antibodies, anti-SSA, anti-SSB, anticardiolipin antibodies, lupus anticoagulant, aß2GP1, anti-dsDNA, anti-Smith antobodies, and anti-ribonucleoprotein antibody positivity were studied as possible predictors for small for gestational age.[35,37,44,48,51,54,56,61,62,64,65,70,74,80,82,84,88,94,99,103] Of these, only active SLE before or during conception showed a significant association and prediction interval for small for gestational age (OR 1·85 [95% CI 1·22–2·81]; $I^2$=0%; figure 5; appendix 1 pp 16–18)

For pre-eclampsia, 29 studies reported associations with at least one of the following predictors: previous lupus nephritis, active SLE before or during conception, secondary antiphospholipid syndrome, chronic hypertension, criteria antiphospholipid, multiparity, anti-SSA,

anti-SSB, lupus anticoagulant, anti-dsDNA, low C3, and low C4 (figure 6).[34,35,37,40,43–45,48,50,60,61,64,65,72,74,76,80,83–85,88–90,92–96,99]

The meta-analyses showed statistically significant associations between the following predictors and preeclampsia: previous lupus nephritis (OR 3·11 [95% CI 2·35–4·12]; $I^2$=0%), active SLE before or during conception (2·32 [1·40–3·83]; $I^2$=0%), and chronic hypertension (5·86 [3·41–10·06]; $I^2$=33%; appendix 1 pp 19–20).

41 studies reported on SLE flares during pregnancy or postpartum (figure 7). SLE flares were defined as changes in Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index, Lupus Activity Index in Pregnancy, SLE Pregnancy Disease Activity Index, or SLE Disease Activity Index 2000 score, or less specific definitions such as onset of new signs or worsening of disease in patients who were previously in remission (figure 7).[106–109] Predictors included previous lupus nephritis, active SLE before or during conception, secondary antiphospholipid syndrome, chronic hypertension, nulliparity, low C3, low C4, criteria antiphospholipid antibodies, anti-SSA, anti-SSB, anticardiolipin antibodies, lupus anticoagulant, aß2GP1, anti-dsDNA, anti-Smith antibodies, and anti-ribonucleoprotein antibody positivity.[34,35,37–41,43–46,50,52,54,55,58,59,61,63,65,68–70,73,74,76,82–86,88,89,92,93,97–102] Chronic hypertension (OR 2·50 [1·74–3·58]; $I^2$=0%) and anticardiolipin antibodies (2·11 [1·38–3·23; $I^2$=0%) were robustly associated with an increased risk of SLE flare during or after pregnancy (appendix 1 pp 21–23). The association between active SLE before or during conception and flares showed high heterogeneity with an $I^2$ above 75%, so effect sizes were not pooled for this predictor.

The predefined subgroup analyses (different SLE diagnostic criteria and SLE with or without secondary antiphospholipid syndrome) were deemed unfeasible because of the insufficient number of eligible studies in each meta-analysis and the absence of adequate comparator groups.

We assessed publication bias by a visual examination of funnel plots when the meta-analysis included a minimum of ten studies (appendix 1 pp 27–28). We did funnel plot assessments for active SLE before or during conception and previous lupus nephritis concerning the livebirth outcome; active SLE before or during conception and secondary antiphospholipid syndrome regarding preterm birth; previous lupus nephritis concerning small for gestational age; secondary antiphospholipid syndrome and previous lupus nephritis regarding the occurrence of pre-eclampsia; and secondary antiphospholipid syndrome, previous lupus nephritis, and anti-SSA

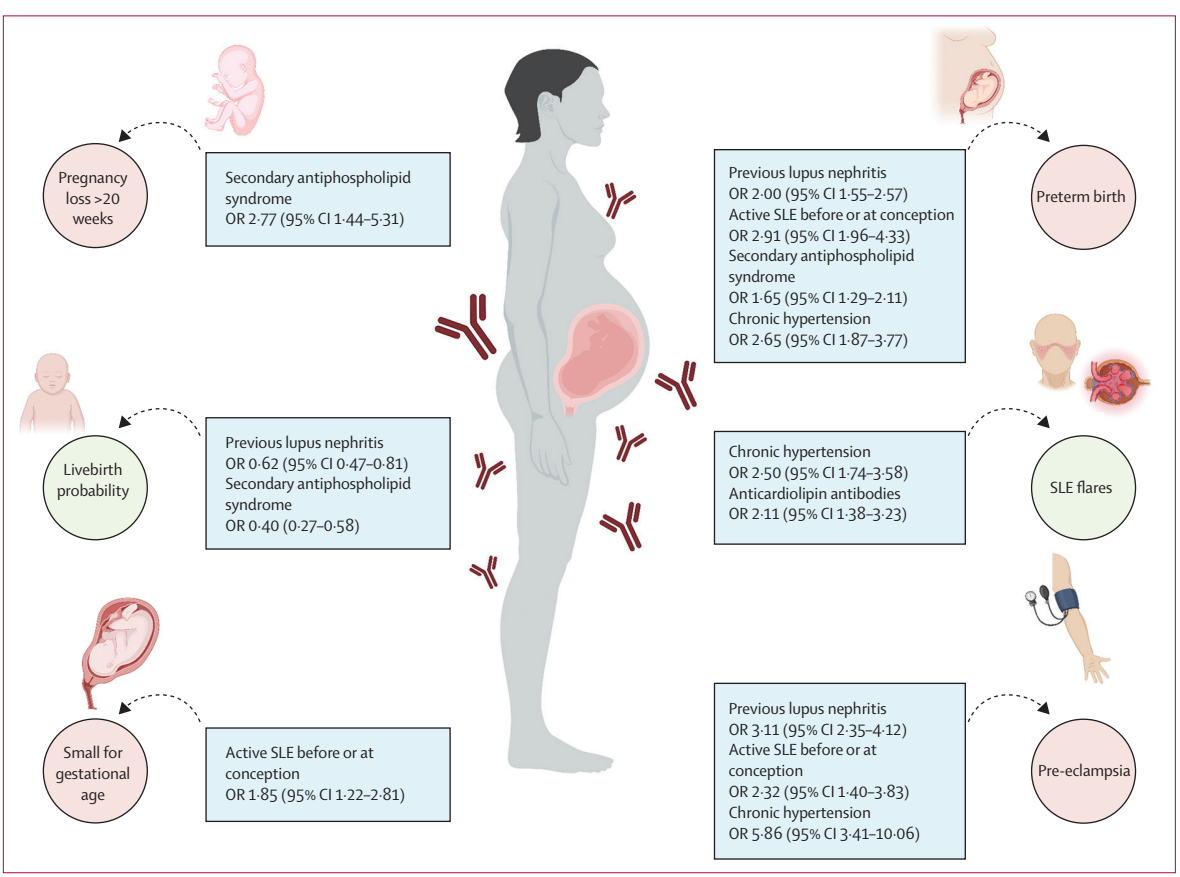


***Figure 8*: Overview of preconception predictors with a significant prediction interval for the respective outcome in pregnant women with SLE**
Created with BioRender.com. OR=odds ratio. SLE=systemic lupus erythematosus.

concerning SLE flares. Potential publication bias was only observed for the positive significant association of lupus nephritis with SLE flare, based on Egger's test and funnel plot asymmetry (appendix 1 pp 27–28). This finding illustrates how smaller studies that found a negative association might not have been published, potentially biasing the results away from the null. Applying the trim-and-fill method[110] to adjust for funnel plot asymmetry indeed showed an adjusted estimate that was slightly closer to the null, yet still statistically significant (OR 1·68 [95% CI 1·22–2·33]; $I^2$=54·3%).

For predictors with an $I^2$ of 50–75% , we did a basic outlier-removal and an influence analysis. Baujat plots and leave-one-out analyses can be found in appendix 1 (pp 29–37). Analyses included active SLE before or during conception and chronic hypertension for livebirth; anti-SSA for pre-eclampsia; previous lupus nephritis and anti-SSA regarding small for gestational age; antiphospholipid antibodies for preterm birth; and previous lupus nephritis, lupus anticoagulant, and parity for SLE flare. Only for previous lupus nephritis with outcomes small for gestational age and SLE flare were outliers detected—ie, the new 95% CI after removal lay outside the 95% CI of the pooled effect estimate. Removing Poh et al (2020)[88] from the small for gestational age meta-analysis of previous lupus nephritis resulted in a statistically significant association where none was found before (OR 1·89 [95% CI 1·34–2·67]; $I^2$=13%). Removing the outlier Fatemi et al (2013)[50] from the SLE flare meta-analysis for previous lupus nephritis, however, did not greatly affect heterogeneity or the statistically significant effect size (appendix 1 p 36). Furthermore, omitting Tani et al[99] from the livebirth meta-analysis of chronic hypertension resulted in a statistically significant association where none was found previously (0·39 [0·19–0·82]; $I^2$=11%).

The overall risk of bias of included studies was substantial (appendix 1 p 38). Specifically, we identified pronounced concerns in two crucial domains: study attrition and study confounding. Study attrition primarily examines the likelihood that the relationship between predictors and outcome are different for completing and non-completing participants. Many of the included studies were judged to have a high risk of bias as they did not clearly describe loss to follow-up. The considerable bias by confounding was primarily caused by a substantial number of studies that consisted of complete case analyses without imputation of missing data and reporting of event rates or univariable analyses. Among the few studies that attempted to adjust for other predictors, adjusting predictors were mostly identified through univariable analysis and retained when they showed statistical significance instead of introduction in the model based on pre-existing literature. Furthermore, most of the studies did not adjust for correlated data (more than one pregnancy per patient) with generalised estimated equation modelling, contributing to the moderate risk of bias in the statistical analysis and reporting domain.

## Discussion

To our knowledge, this study is the first systematic review and meta-analysis with robust pooled effect sizes per individual predictor on adverse pregnancy outcomes and flares during pregnancy in women with SLE. We identified chronic hypertension, previous lupus nephritis, preconception disease activity, and secondary antiphospholipid syndrome as the most important predictors of adverse pregnancy outcomes and flares. To provide an overview of our findings, we summarised predictors and ORs with significant prediction intervals for the respective outcome in figure 8.

This quantification enhances patient-tailored preconception risk assessment for women with SLE, potentially leading to an optimisation of care before and during pregnancy. Consequently, the comprehensive risk assessment of a future pregnancy in patients with SLE can also inform treating clinicians to address modifiable determinants—eg, whenever the risk of disease relapse is deemed too high, individual treatment strategies can be modified, including the continuation of a successful regimen during pregnancy, even if the regimen includes a biologic. Additionally, our results are important when constructing a prediction model for pregnancy outcomes among women with SLE. In model building, the candidate predictor selection must be based on previous literature instead of associations between predictors and outcomes in the study dataset. This meta-analysis thus forms an important foundation for candidate predictor selection for future outcome-modelling studies. Presently, although attempts were made, no such model is accessible for clinical use.[111] The absence of an externally validated prediction model of good prognostic value limits our ability to enhance preconception counselling and the allocation of a patient-tailored treatment plan based on risk stratification.

Notably, we were able to aggregate data for most predictors and important pregnancy outcomes in line with the consensus-based core data set for pregnancy registries in rheumatology.[112] Furthermore, sensitivity analysis showed that few outlier studies individually influenced effect sizes. We pooled predictors that showed a statistically significant association with the following outcomes: livebirth, pregnancy loss after 20 weeks' gestation, preterm birth, small for gestational age, preeclampsia, and SLE flares. The inclusion of prediction intervals augmented the robustness of our findings. Nevertheless, in the case of outcomes such as early pregnancy loss, Apgar scores, low birth weight, and neonatal mortality, we did not identify predictors with significant prediction intervals. Therefore, although the 95% CIs were statistically significant, these associations should be regarded as less robust.

Another important strength of this study is that we incorporated state-of-the-art methods recommended by internationally recognised guidelines for conducting our literature search, data extraction, pooling of data, and assessing the risk of bias.[24–26,28,31] As a result, our findings are applicable to everyday clinical practice. Distinguishing itself from previous reviews on this topic, this meta-analysis provides a comprehensive systematic search across multiple databases without publication date or language restrictions, a blinded standardised screening process, the pooling of ORs, and a risk-of-bias assessment.

We found an association between chronic hypertension (six studies with 965 patients) and anticardiolipin antibodies (seven studies with 781 patients) as predictors for SLE flares. Pooling this data resulted in a pooled OR of 2·50 (95% CI 1·74–3·58) for chronic hypertension and 2·11 (1·38–3·23) for anticardiolipin antibodies, with both exhibiting a significant prediction interval. These predictors are generally less acknowledged as predisposing factors for SLE flares during and outside of pregnancy, compared with other findings in this study. The challenge in differentiating between renal flares and pre-eclampsia might have affected these results, especially in older publications. Future research focusing on pre-eclampsia in patients with SLE might be aided by the use of angiogenic biomarkers, as suggested by the 2021 International Society for the Study of Hypertension in Pregnancy guideline, although their role in diagnosing pre-eclampsia in women with rheumatic disease has yet to be established.[113] Nevertheless, our findings suggest that future studies should focus on these associations and whether true causality exists, which cannot be concluded on the basis of this meta-analysis.

Furthermore, preconception low C3 concentrations were associated with flares showing a pooled OR of 2·36 (95% CI 1·06–5·21) based on four studies involving 439 patients. However, because of factors such as the $I^2$ value of 43%, the prediction interval for this association did not reach statistical significance. Notably, a meta-analysis[114] indicated that a decrease or lack of increase in C3 and C4 concentrations during the first trimester compared with concentrations 6 months before conception were associated with disease flares, underscoring the relevance of dynamic changes in complement concentrations during pregnancy. Furthermore, preconception hypocomplementemia is included in different indices of disease activity, corresponding to the independent predictor of active SLE before or during conception. Unfortunately, the association between active disease before pregnancy and SLE flare in our analysis showed high heterogeneity, so effect sizes for this predictor were not pooled. We encourage the development of studies addressing predictors at different timepoints during pregnancy, as doing so might improve pregnancy outcomes.

The primary focus of this study is on preconceptionally known predictors to enable the use of the results for preconception counselling. Consequently, we (partially) excluded extensive studies in which prediction was done during the first trimester.[13,115,116] Furthermore, important data from large, high-quality, prospective cohorts such as PROMISSE and GR2 could only be included for the outcome of SLE flare, as we had to exclude data on composite adverse pregnancy outcomes and predictors assessed in the first trimester.[13,39,68] Although these data fell outside of the scope of this meta-analysis, these studies are important within the scientific field and in the counselling of women with SLE, as many of the predictors identified in these first-trimester studies (such as hypocomplementemia, anti-SSA and anti-SSB, and anti-dsDNA positivity) are presumed, although not proven, to be applicable in the preconception period as well.

Notably, the multicentre, prospective, observational PROMISSE and GR2 studies, which enrolled women with SLE during and after the first trimester, both identified lupus anticoagulant status as a significant early predictor of a composite of adverse pregnancy outcomes (OR 8·32 [95% CI 3·59–19·26] and 4·2 [1·8–9·7]).[13,68] By contrast, our meta-analysis did not highlight this association, as lupus anticoagulant status had a significant OR only for preterm birth (2·95 [95% CI 1·16–7·49]). These notable disparities in associations should prompt further research because they could be attributed to differences in study populations, missing data, analysis of individual adverse pregnancy outcomes versus a composite, and the timing of prognostication. However, the decision to exclude studies reporting predictors in the first trimester or those with unclear prognostication timing was deliberate. Although this choice might have contributed to differences in associations compared with previous literature, it was intended to minimise heterogeneity in the timing of prognostication in the meta-analysis.

An inevitable limitation of this study is its inclusion of studies with heterogenous data on SLE diagnosis, disease activity, inclusion criteria, and differences in predictor (eg, antiphospholipid syndrome, criteria anti-phospholipid antibodies, and lupus nephritis) and outcome definitions (eg, preterm birth, pre-eclampsia, small for gestational age, and flares). Additionally, other potentially important factors contributing to this heterogeneity include distinctions between planned and unplanned pregnancies, the type of obstetric care provided to women with SLE (eg, high-risk pregnancy clinics *vs* regular obstetric clinics), and medications administered during pregnancy (including SLE-specific treatments or obstetric prophylactic agents such as low-dose aspirin or heparin). These factors might have influenced both the predictors and outcomes addressed in this meta-analysis.

To mitigate these possible forms of bias to the greatest extent possible, we assessed between-study heterogeneity using $I^2$, prediction intervals, and a leave-one-out analysis. In the leave-one-out analysis, two outliers would have resulted in a significant association if they

had been omitted from the analysis. The outlier of Poh et al[88] observed in the small-for-gestational-age meta-analysis could potentially be attributed to several factors, such as a relatively small retrospective cohort size and considerable risk of bias across all domains assessed. However, no explanation was identified for the outlier of the study by Tani and colleagues[99] observed in the livebirth meta-analysis. Importantly, most of the pooled ORs showed low levels of between-study heterogeneity, and some of the pooled ORs showed substantial heterogeneity (12 [13%] of the 92 pooled ORs had an $I^2$ of 50–75%, and five with $I^2 \geq 75\%$ were not reported).

Furthermore, the calculation of absolute risks per predictor on respective outcomes was considered unfeasible because of a substantial number of studies not reporting event rates or contingency tables. Doing meta-analysis on absolute risk in only a subset of available studies imposes a risk of publication or selection bias and is thus deemed unjust, although we acknowledge that absolute risks are of importance in preconception counselling. Another limitation worth acknowledging was our inability to pool ORs for certain important predictors, including socioeconomic factors, BMI, and ethnicity. This limitation arose because of paucity of data, as these variables were rarely detailed in direct association with specific adverse pregnancy outcomes. Additionally, inherent to the study design, only pre-established predictors were included, potentially overlooking other relevant predictors not yet identified by previous studies. Moreover, there was no involvement of individuals with lived experience in this study. Also, although studies were prospective in design, the analysis of several predictors might have been done retrospectively. Finally, for infrequent outcomes like neonatal lupus and congenital heart block, doing a formal meta-analysis was not feasible. These limitations highlight the challenges posed by the availability of data and the rarity of certain outcomes in the included studies.

In conclusion, this systematic review and meta-analysis provides a comprehensive summary of the existing evidence concerning preconception predictors of adverse pregnancy outcomes in women with SLE. These findings are valuable in enhancing the quality of preconception counselling in this high-risk obstetric population and stimulate the development of future prediction model studies, which could facilitate patient-tailored medicine.

#### Contributors

MW, JF, KB, KdL, TL, ML, MS, OT, IW, and JK contributed to conceptualisation. MW, JF, IW, JK contributed to data curation. MW and JF screened for study eligibility, extracted data, and assessed risk of bias. MW, JF, IW, and JK collected the data. MW, JF, IW and JK wrote the initial PROSPERO protocol, including the proposed methods. MW, JF, IW, JK contributed to the formal analysis. MW and JK wrote the original draft. MW and JF contributed to visualisation. JK supervised the study . MW, JF, KB, KdL, TL, ML, MS, OT, IW, and JK contributed to manuscript review and editing. MW, JF, IW, and JK verified the data. All authors had full access to the raw data and had final responsibility for the decision to submit for publication.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

The final data extraction sheet is in appendix 2.

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