

SYSTEMATIC LITERATURE REVIEW – META-ANALYSIS

Preterm Birth and Other Adverse Pregnancy Outcomes in Women With Chronic Kidney Disease: A Systematic Review with Exploratory Meta-Analyses in Lupus and Diabetic Nephropathy

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ABSTRACT

Background: Chronic kidney disease complicates interpretation of pregnancy risk because exposure definitions, denominators, underlying diseases, and clinical practices vary. This review evaluates associations with preterm birth and other adverse pregnancy outcomes while preserving these distinctions.

Objective: To evaluate associations between pre-existing chronic kidney disease and preterm live birth and other adverse maternal and neonatal outcomes, and to determine which disease-specific estimates could be combined without conflating populations, outcome definitions, or crude and adjusted effects.

Methods: PubMed and Europe PMC were searched with supplementary renal disease and microalbuminuria searches. Comparative observational studies were assessed using a prespecified protocol registered as CRD420261503668. Extraction distinguished established CKD, reduced kidney function, and disease-matched comparisons. Exploratory sensitivity analyses used crude risk ratios, restricted maximum likelihood, and modified Hartung–Knapp intervals.

Results: Thirty-four reports were mapped; eight contributed to three disease-matched crude analyses. The prespecified adjusted primary CKD estimate could not be pooled. Pooled risk ratios were 1.12 (95% confidence interval 0.13–9.35) for lupus-nephritis preterm birth, 2.79 (0.84–9.25) for lupus-nephritis preeclampsia, and 1.35 (1.21–1.51) for diabetic-nephropathy cesarean delivery. Adding a quiescent-nephritis cohort yielded a preterm-birth ratio of 1.24 (0.39–3.97). One cohort contributed 92.1% of the cesarean-analysis weight. Certainty was very low.

Conclusion: Diabetic nephropathy was associated with higher crude cesarean-delivery risk, whereas lupus-nephritis estimates remained highly imprecise. Confounding, repeated pregnancies, and restricted evidence availability limit clinical inference.

1. Introduction

Pregnancy in women with chronic kidney disease presents a clinical problem that cannot be represented adequately by a single laboratory threshold. Established kidney damage may coexist with preserved filtration, whereas a creatinine concentration measured during pregnancy reflects both underlying kidney function and gestational physiology. Chronic hypertension, proteinuria, diabetes, systemic autoimmunity, and previous obstetric complications further shape the population encountered in clinical practice. An observational analysis of UK primary care data examined serum creatinine trajectories during and after pregnancy, illustrating the importance of measurement timing and the underlying renal population ¹.

A synthesis intended to inform counseling must therefore distinguish several questions. One concerns the risk associated with established native-kidney disease compared with pregnancies without kidney disease. Another concerns reduced kidney function

defined by a single measurement, which may identify a risk marker without demonstrating chronic disease. A third concerns the additional contribution of nephropathy within an underlying condition, such as systemic lupus erythematosus or type 1 diabetes. Women with the same systemic disease but no recognized nephropathy offer a clinically different comparison from the general obstetric population. Combining these contrasts can obscure the interpretation of a summary effect, even when all studies use the broad label CKD.

Previous systematic reviews have already addressed adverse pregnancy outcomes in CKD. The present review examines disease-specific contrasts and the comparability of exposure definitions and obstetric endpoints. These features complement the broader associations summarized in the 2022 and 2024 reviews. Native-kidney status, live-birth denominators, and overlapping cohorts can materially affect which estimates address the same question ^{2,3}.

Preterm birth is especially vulnerable to apparently small differences in reporting. A numerator describing delivery before 37 weeks may use all deliveries, live births, pregnancies continuing beyond a particular week, or infants as its denominator. A cohort that excludes second-trimester births does not cover the same outcome range as one that includes live births from earlier viable gestations. Similarly, multiple infants from one pregnancy and repeated pregnancies in one woman do not provide independent observations. Such differences affect both the clinical meaning of the estimate and the statistical precision assigned to it.

The interpretation of preeclampsia also depends on the comparator and the background condition. Studies of chronic hypertension may report superimposed preeclampsia, while other studies combine preeclampsia with pregnancy-induced hypertension or eclampsia. In lupus cohorts, the timing of nephritis matters: a history established before pregnancy is distinct from renal involvement emerging during gestation. For diabetes, persistent preconception albuminuria, a single positive early urine test, and clinically established nephropathy represent related but nonidentical exposures. These distinctions were retained rather than removed through statistical harmonization.

The contemporary CKD framework classifies disease by cause, glomerular filtration, and albuminuria, with chronicity requiring abnormalities present for at least three months. This framework clarifies why an isolated abnormal result is insufficient to establish the same exposure as a documented renal diagnosis. In pregnancy research, the timing of the available measurement is equally important: a preconception value can describe baseline status, whereas a later value may already reflect a pregnancy complication. A synthesis should preserve these distinctions even when doing so reduces the number of estimates eligible for pooling ⁴.

Clinical context also differs between autoimmune and metabolic kidney disease. Recent observational studies distinguish active from quiescent lupus nephritis and examine remission status at conception. Their populations demonstrate clinically relevant variation in activity, prior morbidity, and treatment exposure. Consequently, a binary history of nephritis cannot be expected to summarize all clinically relevant variation among pregnant women with SLE. These studies provide a rationale for examining disease-matched contrasts and exposure timing; they do not establish that any particular observational contrast is free of confounding ^{5,6}.

Novelty and aim of the study

The contribution of this review is an explicit separation of the broad CKD question from the narrower lupus-nephritis and diabetic-nephropathy comparisons that the available data can support. Its emphasis is on the

consequences of renal chronicity, outcome-specific pregnancy denominators, cohort overlap, and effect-specific risk of bias for interpretation of pooled results. This is a complementary methodological and clinical contribution to existing CKD reviews, rather than a claim to be the first or a comprehensive replacement for them. The aim was to evaluate associations between pre-existing CKD and preterm live birth and other adverse maternal and neonatal outcomes, and to determine which disease-specific estimates could be combined without conflating populations, outcome definitions, or adjusted and crude effects ^{2,3}.

2. Methods

Protocol and reporting

The review was registered in PROSPERO as CRD420261503668 before numerical extraction. The protocol specified an etiologic review of pre-existing CKD and pregnancy outcomes. Reporting is informed by PRISMA 2020 and PRISMA-S. The reporting distinguishes study populations, confounding, heterogeneity, and analytical decisions. Retrieval ended under a post hoc stopping-rule amendment made after preliminary estimates were available. The amendment restricted the evidence available for synthesis without changing eligibility or the primary outcome. The retrieval and additional-analysis amendments have not been synchronized to the public registry ^{7,8}.

Screening, extraction, and appraisal used a single assessment stream without independent duplication. Missing reports and unresolved numerical values were not imputed, and study authors were not contacted.

Eligibility criteria

The population comprises human pregnancies in any country and healthcare setting. The principal exposure is CKD documented before conception, or detected by 12 completed gestational weeks with evidence supporting antecedent chronic disease. Acceptable sources include persistent kidney damage, a prior clinical diagnosis, and an administrative history whose timing can be evaluated. A single low estimated glomerular filtration rate without evidence of chronicity is classified as reduced kidney function rather than confirmed CKD. Staging based only on an estimate obtained during pregnancy is not treated as equivalent to measured preconception status ⁴.

The comparator is pregnancy without CKD from the same or a sufficiently comparable source population. Disease-specific cohorts are evaluated separately: lupus nephritis is compared with SLE without recognized nephritis, and diabetic nephropathy is compared with diabetes without the renal exposure under study. The principal population excludes kidney transplantation and dialysis already present before conception. Dialysis initiated after conception is not, by itself, a reason to exclude a pregnancy that otherwise meets the baseline criteria. Mixed populations require

a separable relevant subgroup before contributing to a native-kidney analysis.

Eligible designs are comparative prospective or retrospective cohorts and case-control studies, including nested case-control designs. Cohort and case-control estimates are not automatically combined. Case reports, uncontrolled case series, ecological studies, nonhuman studies, and secondary reviews do not supply primary comparative estimates. Secondary reviews can identify additional reports. No publication-year or language restriction was specified. A missing full text is recorded as an access limitation, not as evidence that the study was negative or ineligible. Insufficient reporting can prevent contribution to one outcome without establishing ineligibility for every other outcome.

Outcomes and estimands

The primary outcome is preterm live birth before 37 completed weeks. Extraction records retain the lower gestational boundary, handling of stillbirth, inclusion of multiple pregnancies, and whether the unit is a woman, pregnancy, delivery, or infant. Studies starting observation at 28 weeks are separated from those including earlier viable live births. All-birth and live-birth denominators are not silently equated. The direction of all relative effects is greater adverse-outcome risk or odds in the kidney-disease group when the ratio exceeds one.

Secondary outcomes comprise early preterm live birth before 34 weeks, preeclampsia, small for gestational age below the tenth centile, explicitly defined perinatal mortality, neonatal intensive care admission during the birth hospitalization, and cesarean delivery. Superimposed preeclampsia is separated when reported. A study using a fifth-centile or two-standard-deviation growth threshold is not relabeled as the tenth-centile outcome. Neonatal deaths occurring after a live birth remain part of the live-birth denominator, while a stillbirth is not converted into a live birth because gestational age is reported.

The primary planned estimand is the adjusted odds ratio for preterm live birth associated with CKD versus no CKD. Adjusted risk ratios, odds ratios, hazard ratios, and crude binary comparisons are kept distinct. Odds ratios are not converted to risk ratios for these potentially common outcomes. A model estimating the time to delivery does not become a binary preterm-birth risk model merely because the report labels its coefficient a relative risk. When matching or repeated pregnancies are part of the design, appropriate source estimates and variances are preferred over a reconstruction that ignores that dependence.

Information sources and searches

PubMed and Europe PMC were searched without language or study-design filters. Strategies combined renal-disease concepts with pregnancy and obstetric terms. Broader nephropathy, glomerulonephritis, albuminuria, polycystic-kidney, and explicit

microalbuminuria searches supplemented the initial CKD strategy. Search expressions combined MeSH and title/abstract terms in PubMed and TITLE_ABS fields in Europe PMC; full executable strategies are retained with the search records.

ClinicalTrials.gov and reference lists provided complementary records. Embase, Scopus, and Web of Science were not searched, and WHO ICTRP could not be accessed. PubMed and Europe PMC overlap substantially. Publisher websites, DOI links, PMC, Europe PMC, and institutional repositories were used for report retrieval; OpenAlex was used to locate identified reports.

Record management and selection

Records were deduplicated using bibliographic identifiers and normalized metadata. Eligibility was assessed from titles and available abstracts, followed by accessible source material. Among 1,322 records retained for further assessment, 382 contained abstracts and 940 did not. Decisions on records without abstracts therefore initially relied on titles. Unresolved source or numerical discrepancies precluded inclusion in the corresponding strict synthesis.

Reports were distinguished from underlying cohorts and outcome-specific comparisons. Recruitment centers, dates, and population definitions were compared to identify overlap. Companion reports could inform different outcomes but were not entered as independent estimates of the same outcome. Selection accounting, including nonretrieval and reports awaiting classification, is shown in Figure 1.

Data extraction

Extraction recorded study design, population, renal definition and timing, comparator, outcome criteria, unit of observation, effect measure, event counts, denominator, adjustment factors, and repeated pregnancies. Denominators were assessed separately for each outcome, including the handling of losses, stillbirths, multiple births, and transplant recipients. Conflicting totals were retained as uncertainty rather than treated as resolved.

For Kimmerle, two transplant pregnancies were excluded from the native-kidney cesarean comparison because both were within an impaired-function subgroup in which every pregnancy ended by cesarean delivery. The resulting comparison was 29/34 versus 71/110. Subtraction was not used when subgroup-specific events could not be determined⁹.

Synthesis without pooling

Estimates unsuitable for pooling were grouped by renal exposure, underlying disease, comparator, and outcome. Narrative presentation retained the reported effect measure, adjustment variables, and limitations affecting the estimand. Statistical significance did not determine whether a report was described or whether its direction was considered supportive. Counts of positive and negative studies were not used as an

alternative meta-analysis. Grouping and interpretation were linked explicitly to the contributing evidence and its clinical question.

Risk of bias and certainty

Study selection, comparability, and outcome or exposure ascertainment were assessed using design-specific Newcastle–Ottawa domains¹⁰. The assessment was adapted for the selected effect: comparability reflected adjustment or restriction applicable to that contrast, rather than adjustment in another model from the same report. Maternal age was the first prespecified comparability factor; parity, hypertension, diabetes, multiple gestation, and healthcare access were additional factors where relevant. Singleton restriction or restriction to diabetes could satisfy an additional-factor criterion. SLE matching alone did not satisfy these protocol-specific additional factors.

The assessment comprised 306 criterion-level judgments across 30 cohort and four case-control reports. These are correlated descriptive judgments within reports, not independent quality observations. Criteria without sufficient documentation were classified as unclear. No total-score cutoff or quality-based statistical weight was used. Exposure chronicity, pregnancy-survival selection, repeated observations, and outcome compatibility were considered separately. The quantitative-report display is an adapted NOS-based appraisal, not an unmodified study-quality score.

Certainty was assessed for each displayed association using GRADE domains, starting at low certainty for observational evidence. Imprecision was judged from whether intervals permitted the null and large associations; no numerical minimum clinically important difference was prespecified. Applicability to the disease-specific comparison was distinguished from indirectness for CKD overall. Publication bias could not be assessed statistically; retrieval-related selection was considered separately. Outcome-specific certainty judgments are reported with the results. Certainty concerns confidence in an association for a specified outcome and population; it is distinct from the strength of a clinical recommendation and from a numerical study-quality total¹¹.

Statistical analysis

The three analyses reported here are available-source crude sensitivity analyses. They do not replace the prespecified adjusted primary analysis. Each uses three clinically related cohorts with the same disease-matched comparison and the selected outcome definition. Binary counts were transformed to log risk ratios with their conventional sampling variances. The risk ratio compares a/n_1 in the exposed group with c/n_0 in the comparator group; the sampling variance assumes independent binomial counts. Random effects were estimated using restricted maximum likelihood. Confidence intervals used a modified Hartung–Knapp approach with the variance scaling factor bounded

below by one and a t distribution with $k-1$ degrees of freedom (two for each three-study analysis). The modification prevents a variance multiplier below one from producing an artificially narrower interval than the corresponding unscaled t -based interval. It retains the small-sample uncertainty associated with estimating an average effect from very few studies¹².

Between-study variation was summarized using τ^2 , I^2 , and the heterogeneity Q statistic. Confidence intervals were used to characterize uncertainty in the heterogeneity estimates. I^2 describes the proportion of observed variation attributed to between-study heterogeneity under the fitted model; its interpretation depends on sampling precision and is not a direct measure of clinical similarity¹². Common-effect estimates and conventional Wald intervals from the random-effects model were calculated as model checks, not used to select whichever analysis produced statistical significance. No prediction interval was calculated because each analysis contained fewer than five studies. No funnel plot, regression test of asymmetry, or meta-regression was performed because the available subsets were too small for the prespecified criteria.

Repeated pregnancies were not treated as if a corrected variance had been recovered. Where the original report did not provide an appropriate cluster-adjusted variance for the selected crude contrast, the available counts were used only in the exploratory sensitivity analysis. Restricting the current subsets to unambiguously independent observations left fewer than three studies, so those stricter pooled analyses were not calculated under the protocol. The threshold of three studies was a protocol choice. Individual effects are reported even when a restricted subset is not pooled. Modified Hartung–Knapp intervals do not correct within-woman correlation in the contributing sampling variances.

Analyses used R 4.5.3 and metafor 4.8.0; scripts and aggregate inputs are retained with the analysis data¹². Paule–Mandel, study-weight, and leave-one-out analyses were post hoc. Paule–Mandel estimates with modified Hartung–Knapp intervals were compared with REML; a common-effect model with Wald intervals was used only as an assumption check. REML study weights quantified concentration of information. Leave-one-out analyses were restricted to the expanded four-report lupus-nephritis preterm-birth set, preserving at least three reports in every refit. No two-report leave-one-out pools, meta-regression, or asymmetry tests were added.

3. Results

Study selection

The searches yielded 30,826 records; removal of 7,845 duplicates left 22,981 records for screening. The evidence map comprised 34 reports, including 30 cohort and four case-control reports. Eight reports contributed to three principal exploratory analyses,

and one additional report contributed to an expanded lupus analysis. Reports in the evidence map did not necessarily provide an eligible independent estimate

for every outcome. Figure 1 presents selection accounting.

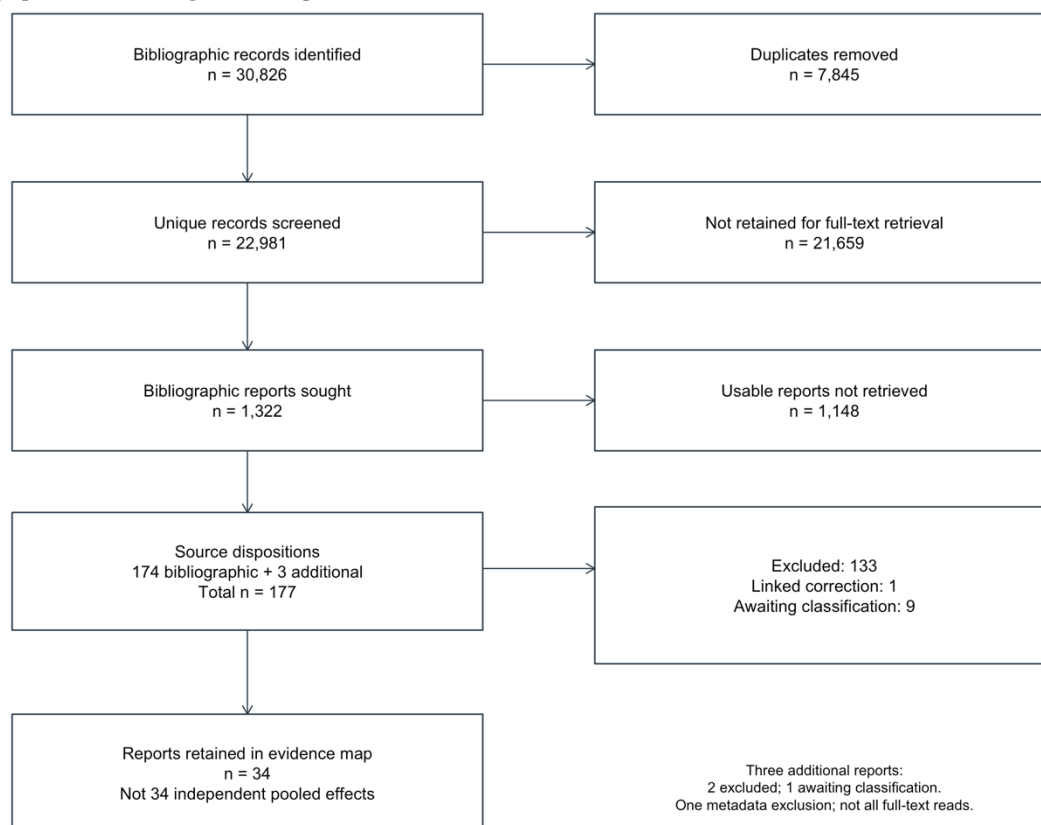


Figure 1. Selection and availability of reports. The evidence map includes linked reports; its count is not the number of independent studies in a pooled analysis.

Characteristics of the quantitative subsets

The clinical comparisons and outcome-specific counts from the eight contributing reports are detailed in Table 1. The lupus-nephritis comparisons arose within SLE cohorts, while the diabetic-nephropathy comparison arose within type 1 diabetes cohorts. The two lupus analyses share the Bramham report.

Therefore, their pregnancy counts cannot be summed as if they represented disjoint participants. The cesarean analysis contains three independent centers but does not eliminate repeated pregnancies within the Kimmerle cohort. All three analyses use crude, outcome-specific counts rather than a mixture of adjusted odds ratios and risk ratios.

Table 1. Studies contributing to the quantitative sensitivity analyses.

Report	Clinical comparison	Selected events / denominator	Principal limitation
Bramham 2011	Prior LN versus nonrenal SLE	PTB 13/43 vs 7/63; PE 12/43 vs 10/64	Repeated pregnancies; baseline KRT not explicit
Clark 2003	Prior renal SLE versus nonrenal SLE	PTB 9/22 vs 19/51	Live-birth total discrepancy; dependence unclear
Zhang 2007	Antecedent LN versus nonrenal SLE	PTB 5/28 vs 58/155	Repeated pregnancies; no adjusted contrast
Mbuli 2015	LN versus nonrenal SLE	PE 10/29 vs 4/32	Exact exposure timing; repeated pregnancies
Shahwar 2026	Prior LN versus nonrenal SLE	PE 26/49 vs 10/76	PTB denominators unusable; KRT NR
Kimmerle 1995	Native DN versus T1DM without DN	CS 29/34 vs 71/110	Two KT removed; repeated pregnancies
Biesenbach 1994	Persistent microalbuminuria versus normoalbuminuria in T1DM	CS 8/12 vs 14/30	Small unadjusted cohort
Klemetti 2016	White F versus B+C+D+R in T1DM	CS 104/108 vs 702/986	Crude comparison across severity classes

LN, lupus nephritis; SLE, systemic lupus erythematosus; DN, diabetic nephropathy; T1DM, type 1 diabetes; PTB, preterm live birth before 37 weeks; PE, preeclampsia; CS, cesarean delivery; KT, kidney transplant; KRT, kidney replacement therapy; NR, not reported. Event counts are outcome-specific. These eight reports support the three displayed sensitivity pools. The broader evidence is described under Scope of the retained evidence map; the expanded analysis incorporates the Wagner subgroup.

The reporting difficulties differed by study. Bramham provided a live-birth denominator that required exclusion of one comparator stillbirth for the preterm outcome. Clark's body and outcome columns supported 73 live births, whereas the abstract and a table caption stated 72. Zhang's report identified nephritis diagnosed years before pregnancy and provided separate live-birth counts. Mbuli's preeclampsia counts could be reconstructed uniquely from the group sizes and reported percentages, but the exact timing of nephritis relative to the protocol boundary remained insufficiently specified^{13,14,15,16}.

Lupus nephritis and preterm live birth

Bramham, Clark, and Zhang supplied 362 pregnancies with the selected live-birth denominators. The respective preterm counts were 13 of 43 versus 7 of 63, 9 of 22 versus 19 of 51, and 5 of 28 versus 58 of 155. The pooled crude risk ratio was 1.122, with a 95% confidence interval of 0.135 to 9.349 and $p=0.8370$. Estimated τ^2 was 0.552, I^2 was 79.0%, and Q was 8.521. The individual and pooled preterm-birth estimates are detailed in Figure 2.

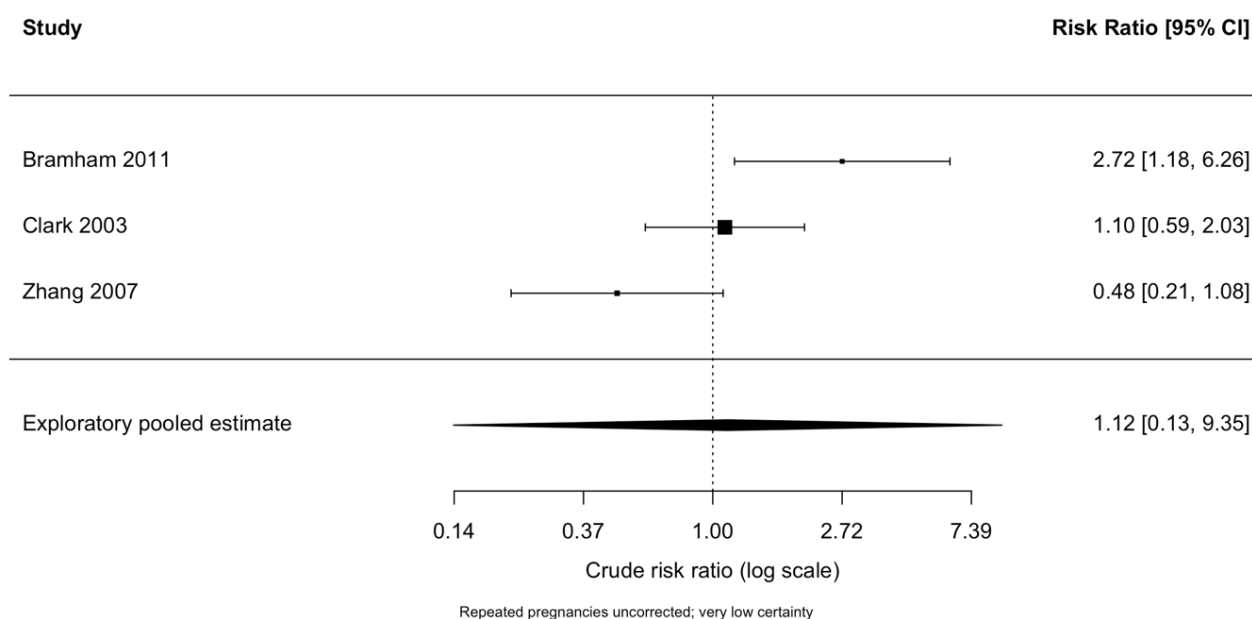


Figure 2. Lupus nephritis and preterm live birth. Available-source crude sensitivity analysis using REML and modified Hartung–Knapp intervals. Crude estimates are exploratory; within-study dependence may affect precision.

The study-level effects varied in direction, and the random-effects interval was wide. The conventional Wald interval was substantially narrower than the modified Hartung–Knapp interval, illustrating the sensitivity of apparent precision to the interval method when only three studies were available. An additional analysis incorporated the Mayo quiescent-at-conception LN subgroup, with 6/15 preterm live births versus 9/39 nonrenal controls. The four-report result was RR 1.243 (95% CI 0.389–3.965; 416 pregnancies; I^2 69.8%). Excluding Clark from that expanded set yielded RR 1.307 (0.137–12.429; 343 pregnancies). Both variants retained missing-outcome and within-woman dependence concerns¹⁷.

Lupus nephritis and preeclampsia

Bramham, Mbuli, and Shahwar supplied 293 pregnancies for the preeclampsia sensitivity analysis. The exposed and comparator event counts were 12 of 43 versus 10 of 64, 10 of 29 versus 4 of 32, and 26 of 49 versus 10 of 76. Preeclampsia was study-defined; a harmonized distinction between superimposed preeclampsia and other diagnoses was unavailable for synthesis. The pooled crude risk ratio was 2.786, with a 95% confidence interval of 0.839 to 9.252 and $p=0.0668$. Estimated τ^2 was 0.076, I^2 was 32.0%, and Q was 2.664. The individual and pooled preeclampsia estimates are detailed in Figure 3.

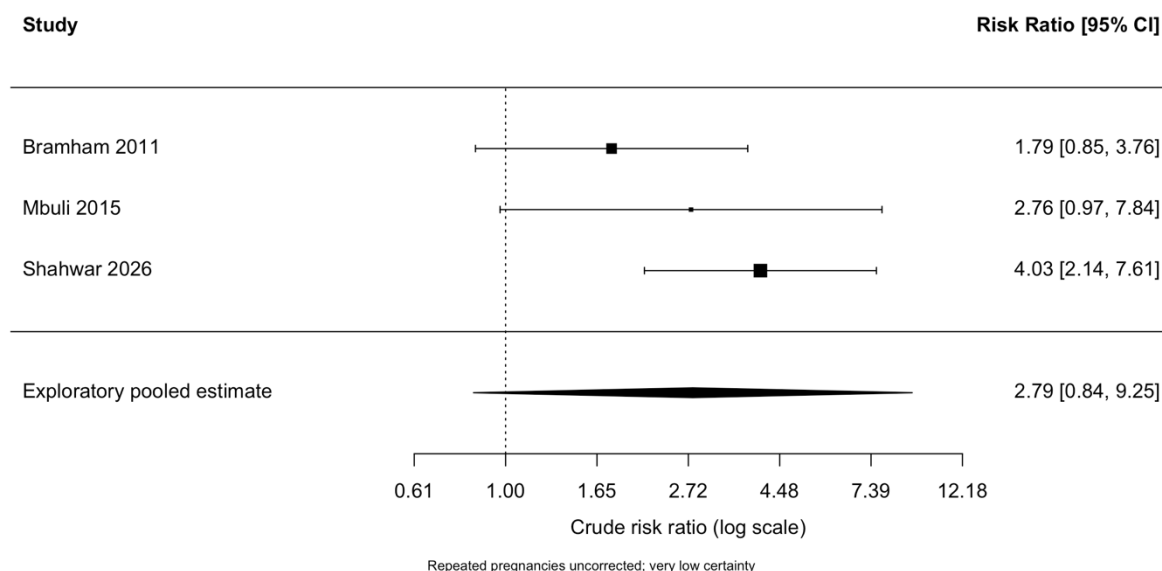


Figure 3. Lupus nephritis and preeclampsia. Available-source crude sensitivity analysis using REML and modified Hartung-Knapp intervals. Crude estimates are exploratory; within-study dependence may affect precision.

Shahwar's nephritis history and treatment before conception supported an antecedent exposure for this comparison. Proteinuria recorded during pregnancy was not treated as proof of baseline nephropathy in its comparison group. The same report's preterm-birth denominators could not be reconciled sufficiently for inclusion in the preterm pool. Removing Mbuli because of uncertain exposure timing left two preeclampsia cohorts and no strict pooled estimate ¹⁸.

Diabetic nephropathy and cesarean delivery

Kimmerle, Biesenbach, and Klemetti supplied 1,280 pregnancies or selected births for the cesarean-delivery comparison. The native-kidney Kimmerle contrast was 29 of 34 versus 71 of 110. Biesenbach reported 8 of 12 versus 14 of 30 in women with persistent preconception microalbuminuria and normoalbuminuria, respectively. Klemetti reported 104 of 108 in White class F compared with 702 of 986

across the combined non-nephropathy classes B, C, D, and R. Shared comparator classes were combined once, not entered as independent studies ^{19,20}.

The pooled crude risk ratio was 1.351, with a 95% confidence interval of 1.205 to 1.515 and $p=0.0077$. Estimated τ^2 and I^2 were both zero, and Q was 0.089. The 95% confidence interval for I^2 extended to 63.0%. The cesarean-delivery comparison is detailed in Figure 4. Klemetti contributed 92.1% of the inverse-variance weight. Its individual crude RR was 1.353 (95% Wald CI 1.281–1.428), compared with the pooled RR of 1.351. Excluding Kimmerle to remove the known repeated-pregnancy cohort left only two studies; no strict pooled estimate was calculated. These data did not provide a pooled adjusted effect separating nephropathy from other determinants of cesarean delivery.

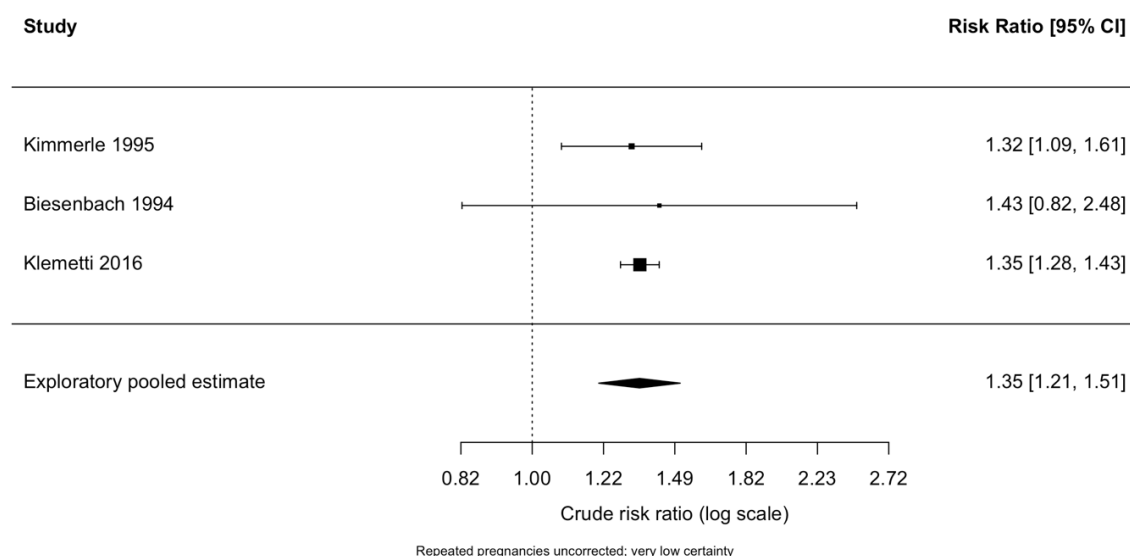


Figure 4. Diabetic nephropathy and cesarean delivery. Available-source crude sensitivity analysis using REML and modified Hartung-Knapp intervals. Crude estimates are exploratory; within-study dependence may affect precision.

The three principal pooled estimates, pregnancy denominators, and heterogeneity statistics are summarized in Table 2. The counts represent outcome-

specific pregnancies or selected births and must not be summed across overlapping analyses.

Table 2. Principal exploratory pooled estimates.

Outcome	k	n	RR (95% CI)	τ^2	I ²	Q	p
LN preterm live birth	3	362	1.122 (0.135–9.349)	0.552	79.0%	8.521	0.8370
LN preeclampsia	3	293	2.786 (0.839–9.252)	0.076	32.0%	2.664	0.0668
DN cesarean delivery	3	1280	1.351 (1.205–1.515)	0.000	0.0%	0.089	0.0077

LN, lupus nephritis; DN, diabetic nephropathy; k, contributing reports; n, outcome-specific pregnancies or selected births. REML models use modified Hartung–Knapp intervals. Shared reports prevent summation of n across outcomes. Certainty is very low for every comparison.

Evidence retained outside the pooled subsets

In the Ontario cohort, preconception creatinine above the 95th percentile was associated with preterm live birth compared with values at or below that percentile (adjusted RR 1.23, 95% CI 1.09–1.38). Adjustment included maternal age, residence, income, region of origin, diabetes, chronic hypertension, and substance-use history. This exposure measures reduced kidney function without necessarily establishing chronic disease. Overlap with another Ontario cohort limits independent aggregation^{21,22}.

Kendrick reported a matched OR of 1.52 (95% CI 1.16–1.99) for preterm delivery in women with clinical or laboratory-defined kidney disease versus matched controls. Matching addressed age, race, diabetes, hypertension, liver disease, and connective-tissue disease. Mixed ascertainment and outcome-denominator limitations prevented treating this estimate as a uniform antecedent-CKD live-birth contrast²³.

The combined North American SLE cohorts reported adjusted ORs of 1.52 (95% CI 0.90–2.57) for preterm

birth and 2.04 (1.01–4.13) for preeclampsia in women with a history of lupus nephritis. Models accounted for age, race, and cohort; one pregnancy per woman was selected. Outcome missingness and overlap with earlier cohorts restricted synthesis. These adjusted odds ratios were not pooled with crude risk ratios²⁴.

In NorDIP, prior clinical nephropathy among women with pre-existing diabetes was associated with small-for-gestational-age birth (adjusted OR 5.88, 95% CI 1.85–18.67). The model included maternal height, gestational age at the first antenatal visit, and third-trimester glycated hemoglobin. Exclusion of antepartum deaths and major anomalies, possible repeated pregnancies, and adjustment for a post-exposure variable limit causal interpretation. These individual associations concern distinct populations and estimands and do not constitute a pooled primary CKD result²⁵.

The separately reported adjusted associations and the reasons they were not combined are detailed in Table 3.

Table 3. Adjusted associations reported outside the pooled subsets.

Report	Exposure and outcome	Reported effect (95% CI)	Interpretive limitation
Harel	Preconception high creatinine; preterm live birth	Adjusted RR 1.23 (1.09–1.38)	Single marker; chronicity unconfirmed; Ontario overlap
Kendrick	Clinical or laboratory renal disease; preterm delivery	Matched OR 1.52 (1.16–1.99)	Mixed ascertainment and denominator limitations
Lucas	Prior lupus nephritis; preterm birth	Adjusted OR 1.52 (0.90–2.57)	Outcome missingness and overlapping cohorts
Lucas	Prior lupus nephritis; preeclampsia	Adjusted OR 2.04 (1.01–4.13)	Age, race, and cohort adjustment; overlap
Glinianaia	Prior diabetic nephropathy; SGA	Adjusted OR 5.88 (1.85–18.67)	Selected survivors; post-exposure glycemia adjustment

OR, odds ratio; RR, risk ratio; SGA, small for gestational age. These source-reported estimates answer different questions and are not pooled with crude risk ratios. The corresponding narrative identifies the adjustment factors and outcome restrictions.

Scope of the retained evidence map

Clinical CKD, chronic glomerulonephritis, assisted reproduction, and congenital renal agenesis formed distinct exposure groups. Lower gestational boundaries, multiple infants per pregnancy, and potentially shared controls prevented uniform interpretation as preterm live birth. The glomerulonephritis cohort reported preeclampsia in

19/64 versus 1/50 pregnancies, but did not define prematurity sufficiently for the primary endpoint^{26,27,28,29}.

Lupus cohorts differed in nephritis activity and timing. The Mayo quiescent subgroup was in remission at conception, whereas active disease could be ascertained before 20 weeks. The Osaka report restricted preterm birth to deliveries after 28 weeks

and contained discordant adjusted estimates. These populations cannot be assumed to represent the same antecedent-nephritis contrast^{17,30}.

Diabetes studies distinguished persistent preconception microalbuminuria, established nephropathy, persistent early albuminuria, and a single early measurement. The Copenhagen preeclampsia regression interval lacked a sufficiently specified confidence level for variance reconstruction. A later model adjusted preterm birth for subsequent preeclampsia, growth, and glycemia. The insulin-trial prognostic analysis did not establish persistent albuminuria, and the Cincinnati analysis concerned time to delivery rather than a binary risk ratio^{31,32,33,34}. Renal-history studies included risk-prediction cohorts with sparse exposure and case-control studies of preeclampsia. Selection by outcome, zero exposed controls, and uncertain renal chronicity limit comparability with cohort risks. Other reports addressed preterm or early-onset preeclampsia, or supplied asymmetric bootstrap intervals. These results were synthesized descriptively rather than combined across incompatible definitions or measures^{35,36,37,38,39,40,41,42,43,44}.

The Korean cohort reported 34/94 versus 171/516 cesarean deliveries and 15/94 versus 20/516 preeclampsia events in women with baseline albuminuria and controls. Its exclusion of second-trimester deliveries limited the preterm outcome. No

pooled estimates were obtained for early preterm live birth, small for gestational age, perinatal mortality, or neonatal intensive care admission⁴⁵.

Risk of bias assessment

Figure 5 presents the adapted NOS-based item profile for nine quantitative reports. The broader appraisal covered 30 cohort and four case-control reports. Comparator-source selection, exposure ascertainment, outcome assessment, and follow-up duration were supported in all nine quantitative reports. Representativeness and absence of the outcome at entry were supported in eight of nine; additional-factor comparability and follow-up completeness in five of nine. None of the nine selected crude contrasts controlled maternal age, although some original reports included age-adjusted models. For example, Bramham reported an adjusted model, but the reconstructed crude RR did not use its adjustment. These item counts describe documentation and the selected contrast, not the probability of unbiased results. In particular, an unadjusted extracted contrast did not inherit control of maternal age from another model in the source report. Repeated pregnancies, uncertain exposure timing, and discrepant outcome denominators were considered separately because the NOS item profile does not fully capture their effects on the pooled analysis. No overall high-quality cutoff or score-based weighting was applied.

Bramham 2011	+	+	+	+	-	+	+	+	+
Clark 2003	+	+	+	+	-	-	+	+	?
Zhang 2007	+	+	+	+	-	-	+	+	+
Mbuli 2015	+	+	+	?	-	+	+	+	?
Shahwar 2026	+	+	+	+	-	-	+	+	?
Kimmerle 1995	+	+	+	+	-	+	+	+	+
Biesenbach 1994	?	+	+	+	-	+	+	+	+
Klemetti 2016	+	+	+	+	-	+	+	+	+
Wagner et al. 2009	+	+	+	+	-	-	+	+	?
	S1	S2	S3	S4	C1	C2	O1	O2	O3
+ Supported ? Unclear documentation - Not supported for selected effect									
Selection S1-S4 Comparability C1-C2 Outcome O1-O3									

Figure 5. Adapted NOS-based appraisal of nine quantitative reports. Comparability applies to the selected crude contrast, not all analyses in the original study. Plus indicates support, question mark unclear documentation, and minus lack of support for the selected effect. S1 representativeness; S2 comparator source; S3 exposure ascertainment; S4 outcome absent at entry; C1 maternal age; C2 additional factor; O1 outcome assessment; O2 follow-up duration; O3 follow-up completeness. Item-level judgments do not establish an overall low-risk classification.

Additional sensitivity and influence analyses

Paule–Mandel estimates closely matched REML for lupus-nephritis preterm birth (RR 1.122, 95% CI 0.134–9.366) and diabetic-nephropathy cesarean delivery (1.351, 1.205–1.515). For lupus-nephritis preeclampsia, the Paule–Mandel estimate was 2.805 (0.934–8.428). A common-effect Wald analysis yielded a narrower preeclampsia interval of 1.834–4.410

around RR 2.844; this comparison changes both the heterogeneity assumption and the interval method. It does not isolate the influence of the heterogeneity estimator. In contrast, the REML–Paule–Mandel comparison holds modified Hartung–Knapp inference constant. Model-specific estimates and intervals are detailed in Table 4.

Table 4. Comparison of statistical models.

outcome	method	k	RR	95% CI lower	95% CI upper	τ^2	I ²	p
LN_PTB	REML	3	1.122	0.135	9.349	0.552	78.975	0.837
LN_PTB	PM	3	1.122	0.134	9.366	0.580	79.799	0.837
LN_PTB	FE	3	1.112	0.728	1.698	0.000	76.530	0.624
LN_PE	REML	3	2.786	0.839	9.252	0.076	31.977	0.067
LN_PE	PM	3	2.805	0.934	8.428	0.041	20.370	0.056
LN_PE	FE	3	2.844	1.834	4.410	0.000	24.926	<0.001
DN_CS	REML	3	1.351	1.205	1.515	0.000	0.000	0.008
DN_CS	PM	3	1.351	1.205	1.515	0.000	0.000	0.008
DN_CS	FE	3	1.351	1.282	1.423	0.000	0.000	<0.001

LN_PTB, lupus nephritis and preterm live birth; LN_PE, lupus nephritis and preeclampsia; DN_CS, diabetic nephropathy and cesarean delivery. REML, restricted maximum likelihood; PM, Paule–Mandel; FE, common-effect model. REML and PM use modified Hartung–Knapp intervals; FE uses Wald intervals. k, contributing reports; RR, risk ratio; CI, confidence interval.

REML weights were broadly distributed in the lupus preterm-birth analysis (31.9–35.9%) and ranged from 21.6% to 43.1% for preeclampsia. Klemetti contributed 92.1% of the diabetic-nephropathy cesarean weight, compared with 7.0% for Kimmerle and 0.9% for Biesenbach. Thus, the apparent precision of that pooled association depended heavily on one cohort. Removing a report from these three-report sets would fall below the protocol pooling threshold.

In the four-report lupus-nephritis preterm-birth set, leave-one-out risk ratios ranged from 0.973 after

omitting Bramham to 1.630 after omitting Zhang. All four confidence intervals included one; I² ranged from 35.9% to 79.0%. The direction of the point estimate was therefore not invariant to study omission, and no refit resolved the substantial uncertainty. The expanded four-report preterm-birth analysis is shown in Figure 6. The effect of omitting each report from the expanded lupus analysis is detailed in Table 5. Uncertainty in the heterogeneity estimates is detailed in Table 6.

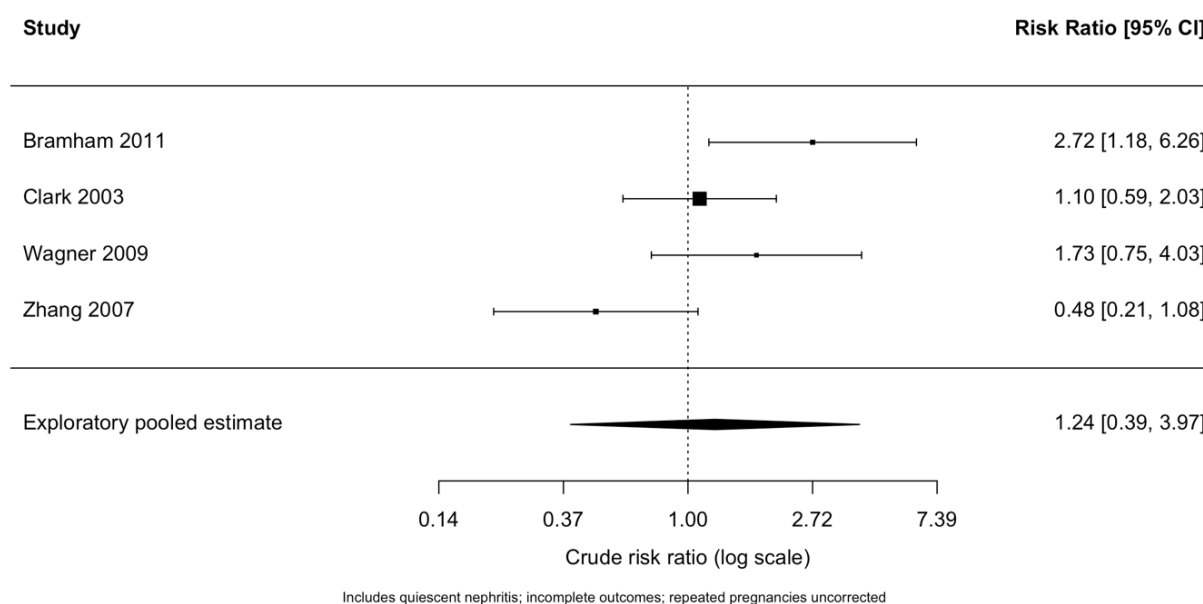


Figure 6. Expanded crude lupus-nephritis preterm-live-birth analysis including quiescent nephritis at conception.

Table 5. Expanded lupus preterm-birth leave-one-out analyses.

omitted	k	RR	95% CI lower	95% CI upper	I2
Bramham 2011	3	0.973	0.203	4.656	60.044
Clark 2003	3	1.307	0.137	12.429	78.063
Wagner 2009	3	1.122	0.135	9.349	78.975
Zhang 2007	3	1.630	0.494	5.381	35.851

LN_PTB, lupus nephritis and preterm live birth; LN_PE, lupus nephritis and preeclampsia; DN_CS, diabetic nephropathy and cesarean delivery. RR, risk ratio; CI, confidence interval; k, contributing reports. Each leave-one-out model retains three reports.

Table 6. Uncertainty in heterogeneity estimates.

Outcome	Parameter	Estimate	95% CI lower	95% CI upper
LN_PTB	τ^2	0.5516	0.0276	29.7622
LN_PTB	I2 (%)	78.9745	15.8108	99.5090
LN_PE	τ^2	0.0758	0.0000	6.4338
LN_PE	I2 (%)	31.9767	0.0000	97.5553
DN_CS	τ^2	0.0000	0.0000	0.0164
DN_CS	I2 (%)	0.0000	0.0000	63.0132

LN_PTB, lupus nephritis and preterm live birth; LN_PE, lupus nephritis and preeclampsia; DN_CS, diabetic nephropathy and cesarean delivery. Intervals quantify uncertainty under the fitted random-effects models; an estimate of zero does not establish absence of heterogeneity.

Sensitivity limits and certainty

The source and dependence restrictions materially limited synthesis. The strict analyses excluding uncorrected repeated pregnancies contained fewer than three studies. No compatible, independent adjusted primary CKD pool was established from the retrieved evidence, and no general-population result was inferred from a disease-matched sensitivity. The additional quiescent-LN analysis and its Clark-exclusion variant remained imprecise. Prediction intervals, asymmetry tests, and meta-regression were

not performed because the number of compatible studies was insufficient. Certainty was very low for all three associations. The main concerns were confounding and repeated pregnancies; preterm-birth estimates also varied in direction, and both lupus intervals permitted large associations and the null. Disease-specific populations further limit applicability to CKD overall. Outcome-specific certainty judgments and the reasons for reduced confidence are summarized in Table 7.

Table 7. Certainty of the disease-specific associations.

Association	Certainty	Principal concerns	Interpretation
Lupus nephritis and preterm live birth	Very low	Confounding and dependence; inconsistent effect directions; very serious imprecision	The interval includes the null and large inverse and positive associations.
Lupus nephritis and preeclampsia	Very low	Confounding, repeated pregnancies, uncertain exposure timing; very serious imprecision	The positive point estimate remains compatible with no association.
Diabetic nephropathy and cesarean delivery	Very low	Confounding and repeated pregnancies; historical and setting-dependent care	No imprecision downgrade based on interval width; one cohort dominates precision.

Observational evidence started at low certainty; no upgrading was applied. All three contrasts are indirect for CKD versus no CKD in the general obstetric population. Retrieval-related selection affects every comparison. Small-study effects were not tested; publication bias was neither demonstrated nor excluded.

4. Discussion

Principal interpretation

The crude cesarean-delivery association in type 1 diabetes was dominated by one cohort, while the lupus-nephritis estimates for preterm live birth and preeclampsia were imprecise. These disease-matched crude associations do not establish causal effects or an adjusted effect for the broader CKD population.

Disease-matched comparisons

The lupus analyses ask about nephritis within SLE, not the overall obstetric burden of SLE compared with the general population. This comparison can reduce some

differences associated with the systemic diagnosis, but it does not guarantee equal disease activity, treatment, hypertension, antiphospholipid status, or access to specialist care. A history of nephritis can also identify a different clinical trajectory from incident renal involvement during pregnancy. When a report defines exposure using renal activity that emerges after conception, an association may incorporate the effect of a gestational complication rather than the prognostic contribution of an antecedent condition.

Likewise, the diabetes comparison does not isolate a uniform renal lesion. Persistent microalbuminuria and clinically established nephropathy may differ in

duration, severity, vascular comorbidity, and management. Combining these exposures in a sensitivity analysis is clinically more coherent than combining them with a healthy general-population comparator, but still leaves meaningful variation. A small estimated between-study variance does not demonstrate that these clinical differences are irrelevant. With only three studies, heterogeneity estimation has limited ability to characterize the range of effects across settings.

The choice of comparator within a classification system also changes the question. Using only the least complicated diabetes class would compare nephropathy with a particularly favorable subgroup. Combining all reported classes without nephropathy produces a broader disease-matched comparison, but does not eliminate differences in retinopathy, disease duration, or treatment history. The present Klemetti calculation used the combined non-nephropathy classes once, making the comparator construction explicit and avoiding repeated use of the same nephropathy group against several correlated controls.

Interpretation of the cesarean association

Cesarean delivery is a clinically important outcome, but it also reflects medical decision-making. An association with nephropathy can arise through maternal or fetal complications, planned timing of delivery, concern about renal deterioration, previous cesarean birth, or local thresholds for intervention. The available crude contrast cannot separate these pathways. The observed association should therefore not be translated into a recommendation for or against cesarean delivery, nor into an estimate of the outcome that would occur if nephropathy itself were prevented while all other characteristics remained unchanged.

Calendar period is also relevant to the comparability of obstetric cohorts. The diabetic studies span different eras of glycemic management and obstetric surveillance. The numerical agreement among their crude relative risks is informative about these particular samples but does not establish that the same absolute risk applies in current practice. Absolute cesarean frequencies in the comparator groups were already substantial and varied between studies. Counseling based on an externally pooled relative effect would require attention to the patient's underlying population and the relevant local baseline risk.

Interpretation of the lupus estimates

The wide preterm-birth interval encompasses markedly different clinical associations. It provides little basis for asserting the absence of a relationship between prior lupus nephritis and preterm birth. The study-level variation and small number of cohorts make the summary sensitive to population composition and the treatment of between-study uncertainty. The modified Hartung–Knapp approach reflects part of that uncertainty, but cannot repair

misclassification or missing data. Its use is a statistical response to sparse synthesis, not a guarantee that the interval captures every source of error.

The preeclampsia estimate also requires careful interpretation. Its point estimate is above one, but the uncertainty is substantial and the data are observational. Describing the result solely as statistically nonsignificant would discard information about both the estimated direction and its imprecision. Conversely, emphasizing the point estimate while minimizing the uncertainty would overstate the finding. The clinically useful statement is that these three available cohorts support an imprecise crude association that remains vulnerable to exposure timing, repeated pregnancies, and confounding.

Renal activity and the clinical interpretation of lupus cohorts

A prior diagnosis of lupus nephritis may remain clinically relevant when renal inflammation is quiescent, but historical disease and active nephritis are not interchangeable exposures. Disease duration, residual proteinuria, renal reserve, and treatment history may differ even among women described as being in remission. The expanded analysis incorporating the quiescent-at-conception subgroup therefore examines one clinically motivated change in the evidence set. Its wide interval does not show that remission has no prognostic value; it shows that this small aggregate comparison cannot estimate that value precisely. No direct comparison of active versus inactive nephritis was produced, and the results cannot identify the optimal timing of conception after a flare^{17,46}.

Recent renal-remission and disease-activity cohorts provide useful context for the lupus findings. Comparisons between women with complete renal remission and those without remission ask a different question from comparing all women with historical nephritis against nonrenal SLE. Likewise, grouping active and quiescent disease separately can reveal clinical variation hidden by a binary renal-history variable. These contextual studies are not added to the present pooled counts. They support more precise exposure descriptions, without supplying a retrospective adjustment for the crude contrasts summarized here^{5,6,46}.

Biopsy and medication-exposure studies further illustrate the range of potential prognostic information. A small retrospective biopsy cohort examined first-trimester proteinuria, histological features, and time between biopsy and conception in relation to preterm delivery. Observational hydroxychloroquine pharmacokinetic work considered adherence as well as physiological changes during pregnancy, while a Japanese tacrolimus study evaluated pregnancy outcomes under treatment. These studies address different clinical questions and are susceptible to selection or confounding by indication. None permits

medication effects or histological risk to be inferred from the pooled nephritis indicator alone ⁴⁷⁻⁴⁹.

Population diversity also matters. The Kaiser Permanente lupus cohort described pregnancy outcomes by ethnicity, antiphospholipid-antibody status, and nephritis history. A California population-based study examined SLE subgroups with cardiovascular events, and a prospective cohort focused on women with previous adverse obstetric outcomes. Differences in the source population, prior pregnancy history, and outcome capture can change the observed baseline risk. Consequently, a disease-matched relative risk should not be transported to another patient population without examining these features ⁵⁰⁻⁵².

Preeclampsia classification presents a related interpretive challenge. The ISSHP recommendations distinguish hypertensive disorders and consider maternal organ dysfunction and uteroplacental dysfunction in the diagnostic framework. In women with pre-existing kidney disease, hypertension and proteinuria may already be present, making the definition of superimposed disease particularly consequential. The historical reports were retained under their reported diagnostic definitions; individual patients could not be reclassified against a single contemporary definition. Thus, apparent agreement in the term preeclampsia does not establish identical ascertainment across cohorts. This limitation concerns outcome measurement as well as biological variation ^{4,53}.

Confounding, selection, and the meaning of the extracted effect

The difference between an adjusted estimate in a source article and the crude estimate selected for synthesis is substantive. A crude risk ratio compares the observed event proportions in the two extracted groups. It does not inherit the covariate balance achieved by a separate regression model, even when both calculations originate from the same participants. Conversely, the presence of a crude contrast in this review does not mean that the original investigators ignored confounding. The adapted appraisal evaluates the estimate used here, while the narrative account retains information about adjusted analyses that address related questions. This distinction prevents a report-level quality label from obscuring the actual analytical contrast.

Adjustment itself requires a clearly defined target. Maternal age or preconception hypertension may describe baseline differences, whereas preeclampsia developing during pregnancy or later fetal growth may lie along a pathway from renal disease to delivery. Adjusting for the latter can change the question from the overall association toward an association conditional on an intermediate event. Such models are not automatically superior because they include more variables. The diabetic-nephropathy reports demonstrate why the timing and role of covariates

should accompany an adjusted estimate. Aggregate published models with different covariate sets cannot be assumed to estimate a single common effect ^{25,32}.

Selection on survival to live birth requires equally careful interpretation. The primary endpoint deliberately describes prematurity among live births, providing a recognizable obstetric outcome. However, pregnancies ending before live birth do not enter that denominator. If renal disease also influences the probability of reaching live birth, the compared live-born groups may represent different selected subsets of the original pregnancies. This possibility cannot be quantified from the extracted counts and should not be treated as an observed bias of known size or direction. It does explain why the live-birth analysis cannot substitute for separate evaluations of pregnancy loss, stillbirth, or perinatal mortality.

Statistical uncertainty and concentration of information

The broad lupus intervals reflect more than the choice of a familiar statistical label. With three reports, the modified Hartung–Knapp calculation uses only two degrees of freedom for inference about the average effect. A point estimate can therefore remain near the center of the individual effects while the uncertainty around that average is substantial. Methodological comparisons support attention to small-sample inference, particularly when study sizes differ, but no interval method resolves incompatibility of outcomes, residual confounding, or dependence within a cohort. The agreement between REML and Paule–Mandel indicates limited sensitivity to that particular estimator choice in these data; it does not validate every other assumption ¹².

The cesarean analysis illustrates a different problem: numerical precision is concentrated rather than broadly replicated. Klemetti supplies most of the information assigned by the model. Its individual crude risk ratio was 1.353 (95% Wald CI 1.281–1.428), close to the pooled point estimate of 1.351. The pooled result consequently expresses the experience of that large cohort to a considerable extent. Agreement with the two smaller reports is descriptively relevant, but their limited weights mean they contribute little protection against a systematic error shared by, or specific to, the dominant study ²⁰.

An I^2 estimate of zero in this setting should therefore not be interpreted as proof of universal consistency. A small set of imprecise studies can be compatible with a range of underlying heterogeneity, as reflected in the heterogeneity confidence intervals. Nor should the positive cesarean association be treated as more causally secure solely because its interval excludes one. Statistical precision and risk of bias answer different questions. The very-low-certainty classification remains appropriate because the selected estimates are crude, some observations are dependent, and applicability varies across clinical eras and populations ^{11,12}.

Relationship to the wider CKD evidence

The broader question remains relevant beyond the two disease-specific settings analyzed here. Clinical CKD, congenital structural disease, prior renal-function measurements, and administrative kidney-disease histories can all identify populations with different obstetric risks. Their comparison with women without CKD requires careful treatment of the exposure definition rather than reliance on a shared diagnostic label. Previous reviews establish the relevance of the question, but this review did not produce a pooled adjusted estimate that can be compared directly with their pooled results ^{2,3}.

Contemporary evidence on renal severity and care

Contemporary CKD studies evaluate several dimensions of renal severity rather than relying exclusively on a diagnostic label. A proteinuria cohort examined graded baseline urinary protein excretion, while prediction studies assessed combinations of blood pressure, biochemical markers, and CKD stage. A separate study compared referred and registered patients, showing why the route into a clinical cohort can affect the characteristics of the observed population. Prediction models from such cohorts require external validation and do not establish causal effects of their component predictors. These findings support retaining proteinuria, hypertension, and ascertainment setting as distinct descriptors in future syntheses ⁵⁴⁻⁵⁶.

The relationship between renal measurements and pregnancy outcomes may also depend on when a sample is obtained. Second-trimester kidney function has been examined in lupus cohorts, whereas a small early-CKD case series evaluated changes in creatinine, blood pressure, and proteinuria during early-to-mid pregnancy. The latter did not establish useful discrimination by its selected warning markers. These results emphasize the need to distinguish a baseline exposure from a changing gestational marker and to avoid assuming that a plausible physiological indicator is necessarily a validated prediction tool ^{57,58}.

Large administrative analyses provide a complementary perspective on preeclampsia and severe maternal morbidity. Analyses of the US National Inpatient Sample assessed kidney-disease subgroups, regional differences, and severe complications during delivery hospitalizations. Their broad coverage is valuable, but diagnosis coding, hospitalization-based denominators, mixed renal categories, and potentially overlapping national samples require attention. Their reported associations cannot be inserted as additional independent observations into the present disease-matched crude analyses ^{59,60}.

Studies of specific glomerular diseases also caution against treating all kidney disease as clinically uniform. A biopsy-proven glomerular-disease cohort largely comprised women with quiescent disease and preserved function. An IgA-nephropathy analysis used

preconception medication patterns as markers of underlying disease control, while a joint maternal-medicine and renal-clinic cohort described outcomes across distinct diagnoses. These studies provide complementary information on baseline status and care setting. Medication proxies cannot establish a causal treatment effect, and the experience of a specialist clinic does not by itself demonstrate the benefit of that clinic relative to a comparable alternative ⁶¹⁻⁶³.

Access to recognition and care is relevant to the meaning of a renal diagnosis in routine data. A US cohort identified under-recognition of laboratory evidence of prepregnancy CKD and gaps in care utilization. A qualitative Australian study documented difficulties obtaining relevant fertility information, and the Hispanic Community Health Study examined self-reported infertility and pregnancy loss in relation to kidney disease. These different designs address diagnostic capture, patient priorities, and reproductive outcomes beyond delivery. They help explain why a hospital-based live-birth cohort describes only one part of the reproductive experience of women with CKD ⁶⁴⁻⁶⁶.

Diagnostic and longer-term context

The overlap between CKD and preeclampsia has prompted exploratory biomarker work. A metabolomic study compared urinary profiles across preeclampsia, CKD, and healthy pregnancy, while another investigation assessed NGAL and KIM-1 as indicators of tubular injury in preeclampsia. These studies support investigation of complementary diagnostic information. They do not validate retrospective reclassification of the historical cases used here, nor establish that a single biomarker resolves the distinction between renal flare and superimposed preeclampsia. The pooled endpoint therefore remains the outcome as defined in the contributing report ^{67,68}.

Longer-term studies address the converse relationship: whether an adverse pregnancy outcome predicts subsequent kidney disease. A national cohort with co-sibling analyses examined later CKD after several obstetric complications. This temporal direction differs from the current question of antecedent renal disease and pregnancy outcome. Such evidence supports considering pregnancy history during later clinical assessment, but cannot be combined with estimates in which CKD precedes conception. Separating these directions avoids presenting a bidirectional clinical relationship as if it were a single causal effect ⁶⁹.

Diabetes treatment and transportability

The diabetic-nephropathy cesarean result should also be interpreted against changes in diabetes management. A randomized automated-insulin-delivery trial improved pregnancy-specific glycemic control, while a smaller randomized pilot evaluated a different closed-loop approach. A prospective comparison of insulin infusion and multiple injections

reported glycemic and neonatal outcomes. Their primary treatment questions differ from nephropathy versus no nephropathy, and glycemic improvement alone cannot be assumed to translate into a proportional reduction in cesarean delivery. They illustrate why historical obstetric associations may not map directly onto outcomes under contemporary treatment⁷⁰⁻⁷².

A population-based diabetes cohort additionally examined obesity and diabetes type, emphasizing differences in maternal characteristics and perinatal outcomes across metabolic populations. Another matched study followed microvascular disease in relatively healthy women with type 1 diabetes during and after pregnancy compared with nonpregnant controls. The latter concerns renal progression rather than the occurrence of obstetric outcomes. Neither comparison supplies an interchangeable nephropathy effect for the current cesarean pool. Together, these studies reinforce the importance of specifying diabetes type, baseline complications, treatment setting, and the direction of the clinical question^{73,74}.

Strengths and limitations

Strengths include outcome-specific denominators, explicit handling of overlapping reports, disease-matched comparisons, and reproducible data and analysis code. Clinical and statistical compatibility determined which estimates could be combined.

Evidence availability was severely restricted, creating a substantial risk of retrieval-related selection bias of unknown direction. Nonretrieval is reported in Figure 1. Nine reports remained unclassifiable and contributed no pooled data. The estimates therefore apply to the accessible subsets and cannot establish comprehensive CKD-associated risks.

Database coverage is another limitation. PubMed and Europe PMC have substantial overlap, while Embase, Scopus, and Web of Science were unavailable. Registry and citation work can complement bibliographic searches but cannot be assumed to compensate fully for absent databases. A repository-location search improves access to known records; it does not establish that all relevant studies have been identified.

Further limitations arise from the observational evidence itself. Crude comparisons leave confounding unresolved. Repeated pregnancies can produce underestimated standard errors when independence is assumed. Restricting an analysis to live births may also change the population under study if kidney disease is associated with pregnancy loss. Although the primary outcome deliberately concerns preterm live birth, that estimand should not be interpreted as the total fetal consequence of CKD across all recognized pregnancies. Separate loss and mortality outcomes require their own denominators and definitions.

Implications for future research

Future primary studies would be easier to synthesize if they report renal diagnosis and chronicity before

conception, baseline transplantation or dialysis separately, and maternal and neonatal denominators explicitly. Reports should distinguish women from pregnancies and infants, identify repeated pregnancies, describe the lower gestational boundary, and state whether stillbirths are included in each outcome. Providing adjusted estimates for prespecified baseline confounders alongside transparent event counts would allow both clinically relevant interpretation and reproducible evidence synthesis without relying on numerical reconstruction.

Priorities for clinically informative evidence

A useful future evidence base would report both relative and absolute outcome frequencies within clinically interpretable renal categories. Preconception renal status should be separated from gestational deterioration, and the presence of hypertension, proteinuria, autoimmune activity, and diabetes should be described at a time relevant to the prognostic question. Delivery outcomes would be more informative if spontaneous preterm labor and medically indicated early delivery were distinguished, because they can reflect different pathways despite sharing a gestational threshold. For cesarean delivery, prior cesarean history and the principal indication would help separate practice patterns from complications associated with nephropathy.

These reporting priorities do not imply that every future study requires the same statistical model. They require sufficient detail to identify the target population, the unit of observation, and the association being estimated. Analyses accounting for multiple pregnancies per woman, with transparent missing-outcome reporting, would improve interpretation of precision. Shared cohort identifiers and recruitment dates would help prevent duplicate contribution across reports. Individual participant data could potentially harmonize definitions and baseline adjustment more closely, but its value would still depend on the completeness and validity of the original measurements. The present aggregate evidence identifies these requirements without claiming that unavailable patient-level information can be reconstructed.

5. Conclusion

Diabetic nephropathy was associated with higher crude cesarean-delivery risk, whereas lupus-nephritis estimates for preterm live birth and preeclampsia remained highly imprecise. The quiescent-nephritis sensitivity analysis did not resolve this uncertainty. All three associations had very low certainty. These findings support further disease-specific investigation but do not establish an adjusted pooled effect for CKD overall.

Declarations

Ethics approval and consent

Not applicable. This study is a systematic review with exploratory meta-analyses of previously published, aggregate data; it did not involve new studies of human or animal participants, so ethics approval and informed consent were not required.

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Conflicts of interest

The authors declare that there are no competing interests.

Author contributions

All authors contributed to the conception and design of the review, the acquisition, analysis, and interpretation of the data, and the drafting and critical revision of the manuscript; all authors approved the final version and agree to be accountable for the work. Harnavi Harun is the guarantor.

Data and code availability

Aggregate extraction data, study-selection records, risk-of-bias judgments, analysis scripts, and statistical outputs are retained in the accompanying data and code package. No individual participant data were obtained. The data have not been deposited in a public repository.

Registration

PROSPERO CRD420261503668.

Generative AI disclosure

The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

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