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SYSTEMATIC REVIEW

# Adverse pregnancy outcomes in pregnant women with chronic kidney disease: A systematic review and meta-analysis

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**Abstract**

**Background:** Chronic kidney disease (CKD) is associated with an increased risk of adverse pregnancy outcomes, but the risk at different stages of CKD (defined by estimated glomerular filtration rate, eGFR) compared with women without CKD has not been quantified in large cohorts.

**Objectives:** To quantify the association between CKD and adverse pregnancy outcomes according to CKD definition, CKD stage and presence or absence of diabetes.

**Search strategy:** A systematic search of EMBASE and MEDLINE from inception to 5 January 2023.

**Selection criteria:** English-language randomised controlled trials as well as cohort and case–control studies investigating adverse pregnancy outcomes in pregnant women with CKD.

**Data collection and analysis:** Two reviewers conducted independent data extractions. A random-effects model was used to estimate risk.

**Main results:** We included 19 studies with 3 251 902 women. Defining CKD using eGFR or serum creatinine produced results with greater effect size but wider confidence intervals. Compared with CKD stages 1–2, women with CKD stages 3–5 have a greater risk, but also greater imprecision in the risk estimate, of the following outcomes: pre-eclampsia (OR 55.18, 95% CI 2.63–1157.68, vs OR 24.74, 95% CI 1.75–348.70), preterm birth (OR 20.24, 95% CI 2.85–143.75, vs OR 8.18, 95% CI 1.54–43.46) and neonatal intensive care unit admission (OR 19.32, 95% CI 3.07–121.68, vs OR 9.77, 95% CI 2.49–38.39). Women with diabetic kidney disease, compared with women without diabetic kidney disease, have higher risks of maternal mortality, small-for-gestational-age neonates, pre-eclampsia and gestational hypertension.

**Conclusions:** There is heterogeneity in the definition of CKD in pregnancy. Future studies should consider ways to standardise its definition and measurement in pregnancy.

KEYWORDS
chronic kidney disease, fetal, maternal, outcomes, pregnancy

## 1 | INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem, with associated morbidity, mortality and reduced quality of life.[1] Globally, the age-standardised prevalence of CKD for women is between 9.6% and 12.5%.[2] Approximately 3%–6% of women of childbearing age are affected by CKD, with 3% of all pregnancies occurring in women with CKD.[3]

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A leading cause of CKD is diabetes mellitus. Diabetic kidney disease affects 2%–8% of pregnancies complicated by pre-existing diabetes,[4] whereas diabetes mellitus is present in 1 in 250 pregnancies.[5]

The stages of CKD are based upon estimated glomerular filtration rate (eGFR), and the grades are based upon proteinuria. Stage-1 and -2 CKD is defined by an eGFR of >60 mL/min/1.73 $m^2$ with markers of kidney damage (e.g. proteinuria).[6] Stages 3–5 have an eGFR of <60 mL/min/1.73 $m^2$ or a urinary albumin-to-creatinine ratio of >30 mg/g.[7] Other methods of assessing CKD include the assessment of damage to the renal parenchyma identified on histopathological examination and renal function, measured prior to or after pregnancy.[8,9]

The assessment of CKD in pregnancy is complicated. The Modification of Diet in Renal Disease (MDRD) study formula and the Chronic Kidney Disease Epidemiology Collaboration (EPI-CKD) formula used to calculate eGFR are not reliable in pregnancy, as the normal range of serum creatinine during pregnancy differs to that outside of pregnancy.[10–12] Therefore, these formulae are not recommended to assess renal function in pregnancy. Furthermore, as many women affected by CKD are not diagnosed before pregnancy, most women will not have had a pre-pregnancy renal function assessment. This lack of assessment coupled with hyperfiltration in pregnancy, which when present interferes with the standard definitions, limits the available information on baseline renal function. Moreover, there is substantial variation in the definition of CKD and its assessment prior to and during pregnancy.

Although the terms diabetic nephropathy and diabetic kidney disease are often used interchangeably, diabetic nephropathy is the classic term used for disease caused by hyperglycaemia affecting the glomerulus, whereas diabetic kidney disease can be considered a broader term that includes disease outside the glomerulus.[13] Much of the older literature used the terminology of diabetic nephrology; however, the terminology of diabetic kidney disease is now thought to better reflect the complexity and heterogeneity of renal disease in diabetic patients.[14]

Previous meta-analyses have acknowledged heterogeneity in the definition of CKD between studies but have opted to combine all studies because of the paucity of data.[15–17] The meta-analyses performed by Zhang et al. and Al Khalaf et al. did not quantify the association between CKD and adverse pregnancy outcomes according to the definition of CKD, though they had quantified the association according to the presence or absence of diabetes.[15,17] Zhang et al. also assessed the effect of CKD stages 1, 2 and 3 on the strength of association.[15] Piccoli et al. focused on pregnant women with immunoglobulin A (IgA) nephropathy alone.[16] Furthermore, these meta-analyses did not differentiate between CKD stages 1–2 and CKD stages 3–5. Owing to these issues, the accurate interpretation of previous systematic reviews in relation to the severity of CKD is limited.[7] Women with diabetes have significantly increased risks of adverse outcomes compared with healthy women, and those with diabetic kidney disease have some of the most complicated pregnancies. However, comparison according to CKD with and without diabetes has not previously been performed. The objective of this systematic review and meta-analysis is to quantify the risk of adverse pregnancy outcomes in women with CKD compared with women without CKD, specifically addressing the varying definitions and stages of CKD, and the presence or absence of diabetic kidney disease.

## 2 | METHODS

### 2.1 | Eligibility criteria

We included studies investigating adverse pregnancy outcomes in women with CKD in pregnancy. Studies must include a control group of pregnant women without CKD for comparison. CKD was defined according to the study definition, which included International Classification of Diseases (ICD) codes/medical records, biopsy, eGFR, serum creatinine and proteinuria. We excluded studies that focused on selected populations (i.e. renal transplantation, systemic lupus erythematosus, multiple pregnancies) and studies that included ten or fewer participants. We included cohort studies, case–control studies and randomised controlled trials only.

### 2.2 | Outcomes

Outcomes investigated included maternal mortality, perinatal mortality (stillbirths and neonatal deaths before 28 days of life), preterm birth (<37 weeks of gestation), early preterm delivery (<34 weeks of gestation), small for gestational age (SGA, below the tenth centile of estimated growth), intrauterine or fetal growth restriction (IUGR/FGR), Caesarean delivery, admission to neonatal intensive care unit (NICU), pre-eclampsia and hypertensive disorders of pregnancy.

### 2.3 | Data source and searches

We searched EMBASE and MEDLINE through the Ovid platform from inception to 5 January 2023 with the support of a clinical effectiveness librarian. The detailed search strategy and search terms are outlined in Table S1. Studies were restricted to human studies reported in English. We manually searched the bibliography of relevant studies and reviews for additional studies that met the inclusion criteria.

### 2.4 | Study selection and extraction

Two reviewers (DJ and BW) independently screened all titles and abstracts that met the inclusion criteria using the

software Rayyan.[18] This was followed by independent full-text screening by DJ and BW. Any conflicts were resolved via discussion with the rest of the team (ML and PW). Independent double data extraction was performed by two reviewers (DJ and BW) and then checked by another reviewer (PW).

### 2.5 | Risk-of-bias analysis

An estimation of the risk of bias of the selected studies was completed using the Brazelli risk-of-bias tool for non-randomised studies and the Oxford Centre for Evidence Based Medicine (OCEBM) grading system.[19,20] Biases were independently assessed by two reviewers (DJ and BW), with conflicts resolved through discussion. Where conflicts could not be resolved by discussion, another member of the team (PW or ML) provided the final decision.

### 2.6 | Data synthesis and analysis

We used Review Manager 5.4 (Cochrane Collaboration) to conduct random-effects meta-analysis. The random-effects model has been chosen because of the significant heterogeneity among the studies included. Where possible, we chose to pool reported adjusted risk estimates from primary studies. When these data were not available, we used raw data to calculate unadjusted risk estimates. The $I^2$ statistic was used to assess statistical heterogeneity, where $I^2$ values of 30%–60% represent a moderate level of heterogeneity. We assessed publication bias by asymmetry testing with funnel plots if there was no evidence of significant heterogeneity.

Subgroup analysis was performed to investigate the impact of study definition of CKD, stages of CKD (in accordance with the Kidney Disease Improving Global Outcomes CKD classification), diabetes, setting (single-centre cohort vs population cohort) and timing (before the year 2000 vs after the year 2000). To be comprehensive, we had not specifically defined CKD at the outset but rather collected the CKD definitions in the literature, which were analysed as subgroups. We also stratified the studies into populations with CKD stages 1–2 and CKD stages 3–5. As a result of the low number of patients with CKD stages 3–5 included in the studies, studies with a study population comprising >30% of patients with CKD stages 3–5 (data extracted using overall study population characteristics) were classed as a CKD stages 3–5 population. If renal function was reported using serum creatinine only, a serum creatinine of >100 μmol/L pre-pregnancy was considered equivalent to CKD stage 3 or above. For the diabetes versus no diabetes subgroup analysis, the study group was women with CKD and diabetes, whereas the control group was women without CKD and with or without diabetes. All studies were classified based on the start and end dates of the study being either prior to the year 2000 or after the year 2000. Studies that crossed over both groups were not included.

### 2.7 | Core outcome sets, patient involvement and registration

No direct patient contact or involvement occurred in this study. No core outcome set (COS) was utilised for this study. There is no published or continuing COS listed for CKD in pregnancy as part of the Core Outcomes in Women's Health (CROWN) initiative.[21] This systematic review has been registered on PROSPERO (CRD42022316391).[22] No amendments have been made to the protocol since registration.

## 3 | RESULTS

### 3.1 | Characteristics of included studies

The initial search produced 2736 search results (Figure S1). After excluding duplicates and non-eligible study designs, a total of 1177 titles and abstracts were screened. Following this, we performed full-text screening and manual searching of bibliography of relevant systematic reviews. A total of 19 studies were included for this review. Six were prospective cohort studies and 13 studies were retrospective cohort studies. Of the retrospective cohort studies, eight were conducted in hospital settings,[23–30] with the remainder being population-based studies. Ten studies were conducted in Europe,[24,27,30–37] four in North America,[26,38–40] three in Australia,[23,28,41] one in South America,[29] and another in Asia.[25] The studies were conducted between 1978 and 2015.

The detailed characteristics of the included studies and study populations are shown in Table S2. We included 3 251 902 women, 26 671 (0.8%) of whom had CKD. The studies reported a median or mean age of between 20 and 41 years. Of the ten studies that reported on ethnicity, 422 223 (89.1%) women were white. There were 148 (0.6%) women with CKD stage 3 or higher.

Various CKD definitions were used across the 19 studies: ten included abnormal levels of eGFR or baseline serum creatinine or creatinine and proteinuria,[23–25,27–30,32,39,42] five used proteinuria or microalbuminuria only,[26,33,35,37,40] three used ICD codes or medical records only,[36,38,41] and one used biopsy results.[34]

### 3.2 | Quality assessment

The majority of the studies included had a reliable method for selecting the non-CKD cohort ($n = 17$), clear inclusion and exclusion criteria ($n = 17$) and a study cohort consisting of women with CKD and only a few other comorbidities ($n = 18$). There was a high risk of bias in the ascertainment of CKD during pregnancy ($n = 7$). Of the six studies that used proteinuria as a measure of CKD, Biesenbach et al. was the only study group that did not define clearly how they differentiated physiological proteinuria from pre-eclampsia.[31]

Overall, the included studies were of moderate quality with a significant risk of bias (Table S3). We performed funnel plots on outcomes that included more than ten publications, which did not suggest publication bias.

### 3.3 | Pooled analysis of CKD and adverse maternal fetal outcomes

Compared with women without CKD, overall, women with CKD had increased risks of preterm birth (<37 weeks of gestation, OR 5.55, 95% CI 3.11–9.92; Figure 1) and early preterm birth (<34 weeks of gestation, OR 2.08, 95% CI 1.67–2.60; Figure S2), Caesarean delivery (OR 2.35, 95% CI 1.45–3.81; Figure S3), FGR or SGA neonates (OR 2.78, 95% CI 1.88–4.12; Figure S4), gestational hypertension (OR 4.74, 95% CI 1.74–12.88; Figure S5) and pre-eclampsia (OR 8.78, 95% CI 3.69–20.89; Figure S6).

Neonates born to women with CKD were 11-fold more likely to be admitted to NICU (OR 11.20, 95% CI 3.29–38.13; Figure S7), compared with neonates born to women without CKD. In addition, women with CKD had a 4.6-fold increase in the risk of perinatal mortality (OR 4.55, 95% CI 1.49–13.86; Figure S8). The risk of maternal mortality was not statistically significant (OR 8.35, 95% CI 0.55–126.11).

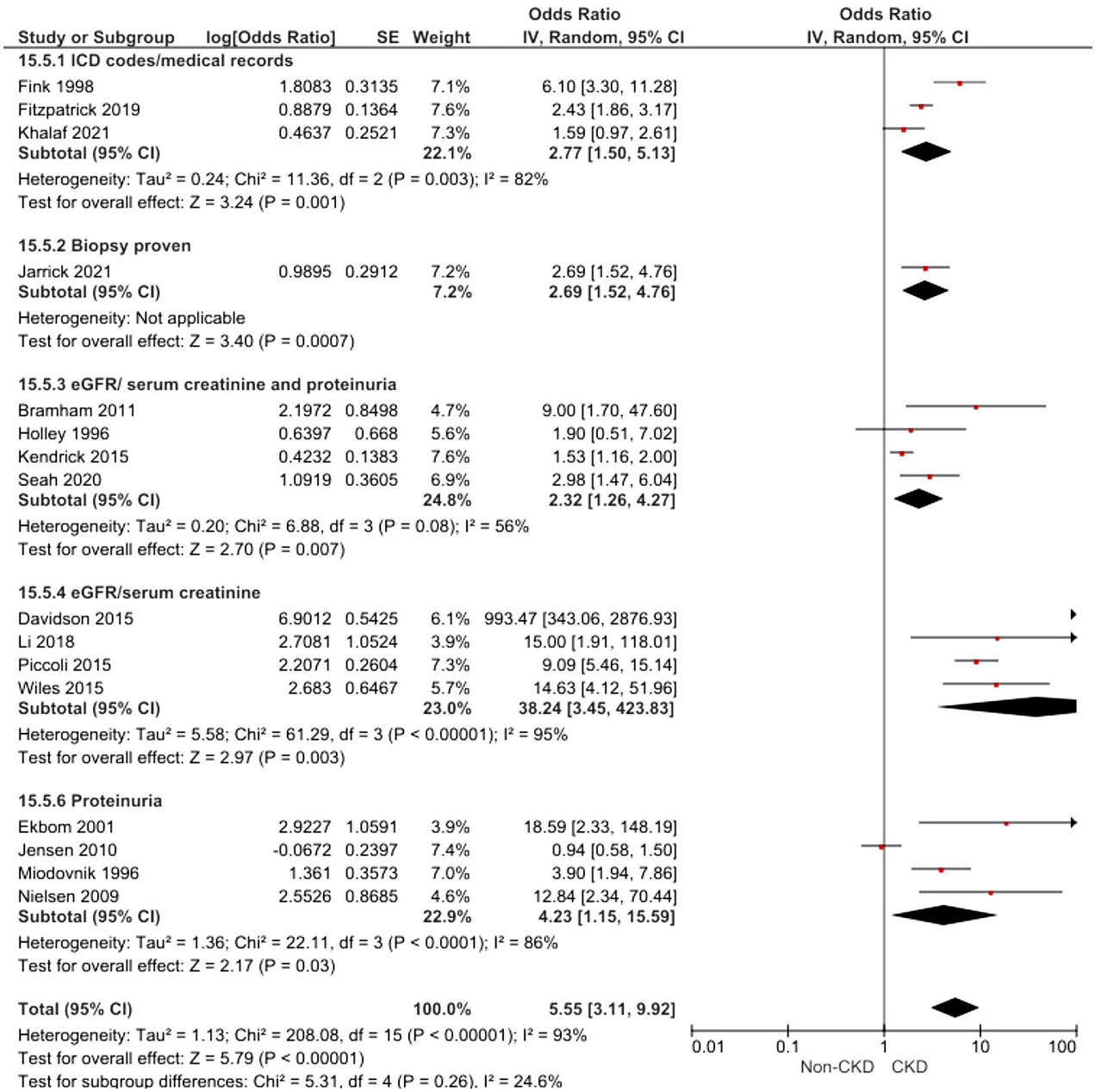


**FIGURE 1** Risk of preterm birth stratified by definition of CKD. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICD, International Classification of Diseases.

### 3.4 | Pre-defined subgroup analysis for method of defining CKD

Subgroup analysis was performed to consider the effects of the definition of CKD (Table 1). In comparison with CKD defined by ICD codes or medical records only, proteinuria only or biopsy only, studies that defined CKD using eGFR or serum creatinine produced results with greater effect sizes but wider confidence intervals across most outcomes: NICU admission (OR 79.27, 95% CI 39.43–159.37), pre-eclampsia (OR 57.18, 95% CI 2.48–1316.79), preterm birth (OR 38.24, 95% CI 3.45–423.83), perinatal mortality (OR 16.51, 95% CI 2.50–108.77), early preterm birth (OR 11.74, 95% CI 6.07–22.71) and Caesarean delivery (OR 7.56, 95% CI 0.64–89.28). Maternal mortality, NICU admission and gestational hypertension outcomes for some definitions could not be calculated because of a lack of studies.

### 3.5 | Pre-defined subgroup analysis for different stages of CKD

Subgroup analyses were also performed to compare studies that included predominantly women with CKD stages 1–2 (67.1%) with studies that had a CKD stages 3–5 population (32.9%) (Table 2). All studies included in the subgroup analysis defined CKD using eGFR,[23,27,30] or using eGFR and albuminuria.[28] Studies including predominantly women with CKD stages 3–5, compared with CKD stages 1–2, reported a higher magnitude but greater imprecision in the risk estimate of preterm birth (OR 20.24, 95% CI 2.85–143.75, vs OR 8.18, 95% CI 1.54–43.46), NICU admission (OR 19.32, 95% CI 3.07–121.68 vs OR 9.77, 95% CI 2.49–38.39) and pre-eclampsia (OR 55.18, 95% CI 2.63–1157.68, vs OR 24.74, 95% CI 1.75–348.70). The outcomes of FGR or SGA neonates, maternal mortality, perinatal mortality, Caesarean delivery, early preterm delivery and gestational hypertension were not statistically significant or were not estimable because of the lack of studies.

### 3.6 | Pre-defined subgroup analysis for studies that focused on diabetic kidney disease

We conducted subgroup analysis to consider the effect of diabetes (Table 2). All studies that focused on diabetic kidney disease defined CKD using either proteinuria only or eGFR/serum creatinine and proteinuria. However, the definition of CKD in studies on non-diabetic kidney disease varied. Compared with women with CKD only, women with diabetes and CKD had higher risks of maternal mortality (OR 35.12, 95% CI 4.44–277.65, vs OR 1.13, 95% CI 0.43–2.94), early preterm birth (OR 6.97, 95% CI 2.73–17.77, vs OR 4.23, 95% CI 1.07–16.72), FGR or SGA neonates (OR 14.11, 95% CI 3.85–51.63, vs OR 3.63, 95% CI 1.74–7.57), pre-eclampsia (OR 10.88, 95% CI 5.45–21.73, vs OR 5.55, 95% CI 2.64–11.68) and gestational hypertension (OR 8.54, 95% CI 3.81–19.13, vs

**TABLE 1** Subgroup analysis with regards to definition of CKD.

| Outcomes | ICD codes or medical records only | Biopsy only | Proteinuria only | Including eGFR or serum creatinine | Including eGFR or serum creatinine and proteinuria |
|---|---|---|---|---|---|
| Maternal mortality | – | – | 43.82 (2.42, 794.57)<br>*n* = 1 | 4.09 (0.19–89.34)<br>*n* = 2 | – |
| Perinatal mortality | 1.16 (0.95–1.42)<br>*n* = 1 | 1.31 (0.25–6.78)<br>*n* = 1 | 2.45 (1.05–5.72)<br>*n* = 4 | 16.51 (2.50–108.77)<br>*n* = 5 | 2.44 (0.67–8.92)<br>*n* = 3 |
| Preterm birth (<37 weeks of gestation) | 2.77 (1.50–5.13)<br>*n* = 3 | 2.69 (1.52–4.76)<br>*n* = 1 | 4.23 (1.15–15.59)<br>*n* = 4 | 38.24 (3.45–423.83)<br>*n* = 4 | 2.32 (1.26–4.27)<br>*n* = 4 |
| Early preterm birth (<34 weeks of gestation) | – | – | 4.35 (2.21–8.55)<br>*n* = 4 | 11.74 (6.07–22.71)<br>*n* = 2 | 1.46 (1.14–1.88)<br>*n* = 3 |
| Small for gestational age/fetal growth restriction | 1.79 (1.05–3.07)<br>*n* = 3 | 1.84 (1.17–2.89)<br>*n* = 1 | 14.53 (2.60–81.07)<br>*n* = 4 | 2.89 (1.25–6.69)<br>*n* = 4 | 4.10 (0.64–26.37)<br>*n* = 3 |
| Caesarean delivery | 1.66 (1.13–2.44)<br>*n* = 3 | 1.74 (1.14–2.66)<br>*n* = 1 | 1.32 (0.67–2.60)<br>*n* = 2 | 7.56 (0.64–89.28)<br>*n* = 3 | 1.41 (1.07–1.86)<br>*n* = 4 |
| Neonatal intensive care unit admission | 3.19 (1.09–9.34)<br>*n* = 2 | – | 43.82 (2.42–794.57)<br>*n* = 1 | 79.27 (39.43–159.37)<br>*n* = 2 | 3.39 (1.15–9.98)<br>*n* = 3 |
| Pre-eclampsia | 3.32 (0.77–14.40)<br>*n* = 2 | 4.29 (2.42–7.60)<br>*n* = 1 | 13.22 (5.61–31.17)<br>*n* = 5 | 57.18 (2.48–1316.79)<br>*n* = 3 | 2.26 (0.74–6.90)<br>*n* = 5 |
| Gestational hypertension | 1.98 (1.49–2.63)<br>*n* = 1 | – | 7.62 (3.59–16.17)<br>*n* = 3 | 1.58 (0.14–17.95)<br>*n* = 1 | 56.19 (3.12–1012.36)<br>*n* = 1 |

*Note*: Values are represented as odds ratio (95% confidence interval). *n*, number of studies.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICD, International Classification of Diseases.

**TABLE 2** Subgroup analysis with regards to CKD stages and diabetic kidney disease.

| Outcomes | CKD stages 1–2 | CKD stages 3–5[a] |
|---|---|---|
| Preterm birth | 8.18 (1.54–43.46) *n* = 4 | 20.24 (2.85–143.75) *n* = 3 |
| Small for gestational age/fetal growth restriction | 7.75 (0.70–85.51) *n* = 3 | 8.40 (0.56–125.42) *n* = 3 |
| Neonatal intensive care unit admission | 9.77 (2.49–38.39) *n* = 3 | 19.32 (3.07–121.68) *n* = 2 |
| Pre-eclampsia | 24.74 (1.75–348.70) *n* = 3 | 55.18 (2.63–1157.68) *n* = 2 |
| **Outcomes** | **Diabetic kidney disease** | **Non-diabetic kidney disease** |
| Maternal mortality | 35.12 (4.44–277.65) *n* = 2 | 1.13 (0.43–2.94) *n* = 1 |
| Perinatal mortality | 2.45 (1.05–5.72) *n* = 4 | 4.33 (1.08–17.43) *n* = 10 |
| Preterm birth | 3.63 (1.40–9.41) *n* = 5 | 5.40 (2.28–12.82) *n* = 11 |
| Early preterm birth | 6.97 (2.73–17.77) *n* = 5 | 4.23 (1.07–16.72) *n* = 4 |
| Small for gestational age/fetal growth restriction | 14.11 (3.85–51.63) *n* = 5 | 3.63 (1.74–7.57) *n* = 11 |
| Caesarean delivery | 1.77 (0.93–3.40) *n* = 3 | 2.50 (1.48–4.22) *n* = 10 |
| Neonatal intensive care unit admission | 11.29 (0.51–249.62) *n* = 2 | 5.77 (1.70–19.61) *n* = 6 |
| Pre-eclampsia | 10.88 (5.45–21.73) *n* = 7 | 5.55 (2.64–11.68) *n* = 11 |
| Gestational hypertension | 8.54 (3.81–19.13) *n* = 4 | 3.55 (0.94–13.39) *n* = 3 |

*Note*: Values are represented as odds ratio (95% confidence interval). *n*, number of studies.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

[a]CKD stages 3–5 included studies with at least 30% of patients having an eGFR of ≤60 mL/min/1.73 $m^2$ or a pre-pregnancy Cr of >100 μmol/L.

OR 3.55, 95% CI 0.94–13.39). However, women with diabetes and CKD had lower risks of preterm birth (OR 3.63, 95% CI 1.40–9.41, vs OR 5.40, 95% CI 2.28–12.82) and perinatal mortality (OR 2.45, 95% CI 1.05–5.72, vs OR 4.33, 95% CI 1.08–17.43), compared with women with CKD alone. The outcomes of Caesarean delivery and NICU admission were not statistically significantly higher in women with diabetes and CKD, compared with women with CKD alone.

## 3.7 | Subgroup analysis based on study setting

We conducted a subgroup analysis comparing single-centre cohort studies with population-based studies and found that single-centre cohort studies reported higher magnitudes of risk, but with greater precision, compared with population studies (Table 3), including for preterm birth

**TABLE 3** Subgroup analysis with regards to setting and timing.

| Outcomes | Single-centre cohort | Population-based study |
|---|---|---|
| Maternal mortality | 35.12 (4.44–277.65) *n* = 2 | 1.13 (0.43–2.94) *n* = 1 |
| Perinatal mortality | 7.53 (2.02–28.10) *n* = 10 | 1.17 (0.96–1.42) *n* = 4 |
| Preterm birth | 8.11 (3.41–19.28) *n* = 12 | 2.41 (1.36–4.29) *n* = 4 |
| Early preterm birth | 6.90 (3.66–13.01) *n* = 8 | 1.31 (1.01–1.71) *n* = 1 |
| Small for gestational age/fetal growth restriction | 9.22 (1.84–46.29) *n* = 12 | 1.86 (1.19–2.91) *n* = 4 |
| Caesarean delivery | 2.59 (0.85–7.88) *n* = 9 | 1.70 (1.28–2.25) *n* = 4 |
| Neonatal intensive care unit admission | 13.31 (2.49–71.02) *n* = 7 | 3.16 (1.08–9.22) *n* = 2 |
| Pre-eclampsia | 14.20 (3.58–56.26) *n* = 12 | 2.59 (1.36–4.95) *n* = 4 |
| **Outcomes** | **Before the year 2000** | **After the year 2000** |
| Maternal mortality | 35.12 (4.44–277.65) *n* = 2 | 1.13 (0.43–2.94) *n* = 1 |
| Perinatal mortality | 5.92 (2.00–17.49) *n* = 6 | 7.42 (0.90–61.34) *n* = 6 |
| Preterm birth | 3.25 (1.21–8.72) *n* = 5 | 12.77 (3.04–53.53) *n* = 7 |
| Early preterm birth | 18.32 (3.83–87.51) *n* = 5 | 6.50 (2.56–16.48) *n* = 5 |
| Small for gestational age/fetal growth restriction | 7.79 (2.90–20.89) *n* = 5 | 3.36 (1.34–8.43) *n* = 6 |
| Caesarean delivery | 2.20 (1.52–3.17) *n* = 6 | 4.28 (0.51–36.18) *n* = 4 |
| Neonatal intensive care unit admission | 16.67 (2.56–108.69) *n* = 3 | 13.33 (1.39–127.90) *n* = 4 |
| Pre-eclampsia | 10.72 (6.22–18.48) *n* = 8 | 7.00 (0.38–127.63) *n* = 5 |

*Note*: Values are represented as odds ratio (95% confidence interval). *n*, number of studies.

(OR 8.11, 95% CI 3.41–19.28, vs OR 2.41, 95% CI 1.36–4.29), early preterm birth (OR 6.90, 95% CI 3.66–13.01, vs OR 1.31, 95% CI 1.01–1.71), FGR or SGA neonates (OR 9.22, 95% CI, 1.84–46.29, vs OR 1.86, 95% CI 1.19–2.91), NICU admission (OR 13.31, 95% CI 2.49–71.02, vs OR 3.16, 95% CI 1.08–9.22) and pre-eclampsia (OR 14.20, 95% CI 3.58–56.26, vs OR 2.59, 95% CI 1.36–4.95).

## 3.8 | Subgroup analysis based on timing

A subgroup analysis for studies prior to and after the year 2000 was also performed (Table 3). We observed that compared with studies conducted after the year 2000, studies

conducted before the year 2000 had a higher risk of early preterm birth (OR 18.32, 95% CI 3.83–87.51, vs OR 6.50, 95% CI 2.56–16.48), FGR or SGA neonates (OR 7.79, 95% CI 2.90–20.89, vs OR 3.36, 95% CI 1.34–8.43) and NICU admission (OR 16.67, 95% CI 2.56–108.69, vs OR 3.36, 95% CI 1.39–127.90), but a lower risk of preterm birth (OR 3.25, 95% CI 1.21–8.72, vs OR 12.77, 95% CI 3.04–53.53).

# 4 | DISCUSSION

## 4.1 | Main findings

Our systematic review and meta-analysis of 19 studies included over 3.2 million women and 26 671 women with CKD. To our knowledge, our study is the first to assess the impact of variation in the definition of CKD used among studies on the derived risk estimate in the meta-analysis. We found studies that defined CKD using eGFR or serum creatinine produced results with greater effect sizes but wider confidence intervals, compared with studies that defined CKD with ICD codes, biopsies, serum creatinine or eGFR and proteinuria. In our subgroup analyses, we show that women with diabetic kidney disease have higher risks of adverse pregnancy outcomes, including a 35-fold increase in the risk of maternal mortality, in comparison with women with CKD. We also confirm that women with CKD stages 3–5 have an increased risk of preterm birth, pre-eclampsia and NICU admission, compared with women with CKD stages 1–2. Our subgroup analysis on the setting and timing showed that studies conducted in single centres before the year 2000 had higher risks of adverse pregnancy outcomes, compared with population-based studies conducted after the year 2000.

## 4.2 | Strengths and limitations

The main strength of our study is our subgroup analysis on CKD definitions, CKD stages and diabetic kidney disease to facilitate a clearer clinical interpretation. Our large sample size resulted from a comprehensive search that included all relevant systematic reviews to date. Our robust methodology included the use of separate reviewers to conduct independent screening, data extraction and quality assessment. We had strict inclusion and exclusion criteria and excluded patients with renal transplantation and systemic lupus erythematosus nephropathy. This is because patients in both populations are often subject to severe immunosuppression which would introduce selection bias to our study.

The potential for confounding by proteinuria, the use of eGFR in pregnancy and dynamic serum creatinine levels in pregnancy could not be completely adjusted for or excluded, which increases the bias in our review. Other potential unmeasured confounding factors could have affected the association of CKD with the measured adverse pregnancy outcomes, such as diabetes control, blood pressure control, concomitant prescription drug usage in pregnancy and family history. Another limitation is our definition of studies on CKD stages 3–5. With the low number of patients with CKD stages 3–5, we classified a study as performed in a population with CKD stages 3–5 if the study population consisted of >30% of patients with CKD stages 3–5. This was an arbitrarily selected threshold, as most of the included studies either did not report the CKD stage of their study population, owing to their method of CKD definition, or predominantly had a study population comprising patients with CKD stages 1–2. Other limitations include potential publication bias because the review was limited to studies reported in English language only and the lack of inclusion of grey literature. We were unable to systematically control for confounding as we could not stratify by adjusted and unadjusted risk ratios because of a lack of adjusted data. Adjusting for potential confounding factors, such as age, ethnicity, body mass index and socio-economic status, would have been helpful to ascertain whether the observed association is affected by confounding. As a proportion of the included studies were retrospective, it is possible that the data collected was limited through incomplete, inaccurate or inconsistent historical data, which could have affected whether the case and control groups were ascribed correctly. To further complicate the situation, the heterogeneity between the study designs can potentially overestimate or underestimate the association between CKD and adverse outcomes through differences in study population.

## 4.3 | Interpretation

In keeping with current literature, our pooled analysis showed that CKD is associated with an increased risk of perinatal mortality, preterm birth, gestational hypertension, pre-eclampsia, SGA neonates, Caesarean delivery and NICU admission. Zhang et al. and Khalaf et al. also investigated the impact of CKD on adverse pregnancy outcomes.[15,17] Both meta-analyses indicated that CKD is associated with an increased risk of preterm birth, Caesarean delivery, pre-eclampsia and SGA neonates. Khalaf et al. reported that the cause of the kidney disease might confer different risks in pregnancy.[17]

The heterogeneity in CKD definition limits the value of the outcomes measured in previous meta-analyses, as the meta-analysis of data collected using different CKD definitions produces information of limited clinical significance. In this study, we found that the use of eGFR or serum creatinine to define CKD produced results with greater effect sizes but wider confidence intervals, compared with other definition groups, such as using ICD codes to define CKD, across most outcomes. During pregnancy, serum creatinine, eGFR and proteinuria all change dynamically, which limit their clinical value for diagnosing CKD in pregnancy. In this study, we noted that only a few studies had pre-pregnancy measurement and serial measurements throughout various time points in pregnancy.

Most of the included studies only had a single measurement in patients previously diagnosed with CKD, which limits the internal validity of these studies. Furthermore, there were no details on how the patients were diagnosed with CKD initially. CKD is often under-recorded as CKD can be difficult to diagnose.[43]

As eGFR is not validated for use in pregnancy, creatinine clearance in pregnancy has been suggested for assessing renal function; however, it is cumbersome, time-consuming and impractical on a large scale, as it requires 24 h of urine collection. Therefore, some practitioners prefer to use serum creatinine to assess renal function in pregnancy.[10] However, we would still face the issues of pregnancy-related changes in creatinine clearance, the classification of severity and the identification of appropriate thresholds. As such, there is a need to identify more accurate methods for assessing renal function during pregnancy. Alternatively, a better understanding of the interpretation of gestational changes in eGFR during pregnancy and its association with pregnancy outcomes could improve the clinical utility of eGFR. This might be useful, as eGFR is widely used, easily available and familiar to clinicians.

Our subgroup analysis demonstrated that pregnancies affected by diabetes and CKD are at a higher risk of FGR or SGA neonates, compared with non-diabetic CKD pregnancies. In contrast, women with diabetes during pregnancy, especially those without optimal glycaemic control, are usually at risk of having large-for-gestational-age babies or macrosomia.[44] One possible explanation may be the cardiovascular remodelling associated with poor glycaemic control.[45] If maternal glycaemic control was suboptimal and persisted for prolonged periods during pregnancy, placental insufficiency may occur and lead to FGR or SGA neonates.[46] Unfortunately, the degrees of adequate glycaemic control were not fully reported in the studies we assessed to confirm the underlying mechanism for this association. Another potential mechanism may be related to the association of CKD with pre-eclampsia, which is known to be associated with FGR caused by placental dysfunction.[47]

Although we found a 35-fold increase in the pooled risk of maternal mortality in diabetic kidney disease, there was only a small number of women who died. Moreover, there were inherent differences between single-centre cohort studies and the population studies. Interestingly, our study found that pregnant women with CKD and diabetes were not at a higher risk of preterm delivery, Caesarean delivery, perinatal mortality or having newborns that needed NICU admission, compared with pregnant women with CKD alone. This could be associated with increased antenatal surveillance in women with CKD and diabetes.

In our subgroup analysis of CKD stages, we found that women with CKD stages 3–5 had a higher risk of preterm birth, NICU admission and pre-eclampsia, but not of SGA neonates. These findings are in keeping with those reported by Khalaf et al.[17] It is worth noting that the estimated effect for CKD stages 3–5 had wider confidence intervals compared with that for CKD stages 1–2. Although CKD stages 1–2 had an increased risk of adverse pregnancy outcomes, this is a population with a relatively normal GFR and there may be confounding from the cause of CKD. For example, diabetes mellitus is independently associated with adverse pregnancy outcomes.[44] Further risk of bias arises from the underestimation of renal function using calculated eGFR in pregnancy, which is not currently recommended for clinical use.[10]

Our subgroup analysis on setting suggest that single-centre cohort studies produced higher risk estimates that are more imprecise. This may be because single-centre cohort studies are smaller in scale compared with population-based studies. For the subgroup analysis on time, studies conducted before the year 2000 generally had higher risks of adverse pregnancy outcomes, except for preterm birth, compared with population-based studies conducted after the year 2000. The effects observed cannot be attributed to a specific intervention or change in practice but may reflect the general improvement in care over time. We speculate that the higher level of preterm birth in the more recent studies may be associated with the trend over time of more women with complex medical comorbidities now conceiving.

## 5 | CONCLUSION

There is heterogeneity in the definition of CKD in pregnancy. In the future, researchers need to consider ways to standardise the definition and measurement of CKD. As there are only limited options for assessing renal function during pregnancy, there is a need to develop new or modify existing methods of assessing renal function. Furthermore, as serum creatinine is not tested in all pregnancies, and ideally should be quantified prior to pregnancy, the diagnosis of CKD in pregnancy remains challenging. As serum creatinine is a relatively inexpensive test and can provide earlier diagnosis and management of CKD in pregnancy, routine serum creatinine measurement in all pregnant women should be considered by policymakers, as it would improve care for CKD in pregnancy and has been shown to be feasible in early pregnancy.[48] As all women with CKD should have regular follow-up appointments to monitor for complications in pregnancy, we suggest that women considered at very high risk within the CKD group should have even more strict follow-up with increased antenatal surveillance.

### AUTHOR CONTRIBUTIONS

The systematic review was conceptualised following literature review and discussion amongst PW, ML, KB, RF and DJ. All team members (PW, ML, KB, RF, DJ and BW) were involved in creating the protocol, screening, data extraction, analysis, creation of the report and writing the article for publication.

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## CONFLICT OF INTEREST STATEMENT
The authors report no conflicts of interest.

## DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## ETHICS APPROVAL
No ethics approval was required.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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