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Authors	Al Khalaf, Sukainah;Bodunde, Elizabeth O.;Maher, Gillian M.;O'Reilly, Éilis J.;McCarthy, Fergus P.;O'Shaughnessy, Michelle M.;O'Neill, Sinéad M.;Khashan, Ali S.
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Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Sukainah Y. Al Khalaf[1,2], Elizabeth Bodunde[1], Gillian M. Maher[1,2], Éilis J. O'Reilly[1,3], Fergus P. McCarthy[2,4], Michelle M. O'Shaughnessy[5], Sinéad M. O'Neill[6], Ali S. Khashan[1, 2]

[1] *School of Public Health, University College Cork, Cork, Ireland*

[2] *INFANT Research Centre, University College Cork, Ireland*

[3] *Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA*

[4] *Department of Obstetrics and Gynaecology, Cork University Hospital, Cork, Ireland*

[5] *Department of Renal Medicine, Cork University Hospital, Cork, Ireland*

[6] *School of Public Health Alumna, Cork, Ireland*

Corresponding authors: Sukainah Al Khalaf, MPH. alkhalaf.sukainah@gmail.com and Ali S. Khashan,PhD. a.khashan@ucc.ie

Abstract

Objective: Limited evidence exists on the role that the cause of CKD plays in determining pregnancy outcomes. The aim of this systematic review and meta-analysis was to examine the association between CKD and adverse pregnancy outcomes, by cause and severity of CKD where reported. The protocol was registered on the International Prospective Register of Systematic Reviews (CRD:42020211925).

Data sources: PubMed, Embase, and Web of Science were searched until May 24, 2021, supplemented with reference list checking.

Study eligibility criteria: Studies that compared pregnancy outcomes in women with or without CKD were included. Two reviewers independently screened titles, abstracts, and full-text articles according to *a priori* defined inclusion criteria.

Study appraisal and synthesis methods: Data extraction and quality appraisal were performed independently by three reviewers. The GRADE approach was used to assess the overall certainty of the evidence. Random-effects meta-analyses were used to calculate pooled estimates using the generic inverse variance method. Primary outcomes included pre-eclampsia, Caesarean section (CS), preterm birth (PTB) [<37 weeks' gestation] and small for gestational age (SGA) babies.

Results: Of 4,076 citations, 31 studies were included. Pre-pregnancy CKD was associated significantly with a higher risk of pre-eclampsia [pooled crude odds ratio (OR): 8.13, (95% confidence interval (CI), 4.41–15), and adjusted OR (aOR): 2.58, (1.33–5.01)], CS [aOR: 1.65, (1.21–2.25)], PTB [aOR: 1.73, (1.31–2.27)] and SGA [aOR: 1.93, (1.06–3.52)]. The association with stillbirth was not statistically significant [aOR: 1.67, (0.96–2.92)]. Subgroup analyses indicated that different causes of CKD might confer different risks and that severity of CKD is associated with risk for adverse pregnancy outcomes, as pregnancies with later stages CKD, compared to earlier stages, had higher odds of pre-eclampsia, PTB and SGA. The GRADE certainty of the evidence was 'very low'.

Conclusions: This meta-analysis quantified associations between pre-pregnancy CKD, overall and according to cause and severity, and adverse pregnancy outcomes. These findings might support clinicians aiming to counsel women with CKD, by allowing them to tailor their advice according to the cause and severity of CKD. We identified gaps in the literature, and further

studies examining the effect of specific kidney diseases and other clinical characteristics (e.g. proteinuria, hypertension) on adverse pregnancy outcomes are warranted.

Introduction

Chronic kidney disease (CKD) is a major global public health problem associated with excess morbidity, decreased quality of life, and premature mortality (1). Definitions and classifications of CKD have changed over time, with the current international guidelines defining CKD as having markers of kidney damage (e.g., albumin excretion rate >30 mg/d) and/or a reduced glomerular filtration rate (GFR)<60 mL/min/1.73 m^2 for at least three months duration, irrespective of the underlying cause (2, 3). The disease is then sub-classified into five stages according to the level of kidney function, stages 1-2 (mild CKD with an eGFR≥60 mL/min/1.73 m^2 but with other evidence of kidney damage, such as proteinuria or structural kidney abnormalities), and stages 3-5 (moderate to severe CKD, with GFR<60 mL/min/1.73 m^2) (2, 3). A global prevalence of 9.5% has been reported for CKD in women overall, with a higher proportion of early stages of the disease reported in women than men (1, 4). In women aged 20-39 years, the prevalence of stages 1-2 and stages 3-5 CKD are estimated to be 3% and 0.67%, respectively (5, 6).

Prior reports, many of them small in size and emanating from single centres, have shown associations between CKD and adverse pregnancy outcomes (5, 7, 8). However, associations of adverse pregnancy outcomes with the cause of CKD are less known. The most recent meta-analysis assessing the association between CKD and adverse pregnancy outcomes included 14 studies published between 1979 and 2013 (8). Investigators reported higher odds of pre-eclampsia, caesarean section (CS), preterm birth (PTB), and small for gestational age (SGA) or low birthweight (LBW) in women with CKD compared to women without CKD (8). However, eight of the 14 studies examined adverse pregnancy outcomes among women with diabetes (diabetic nephropathy as an exposed group), which makes it difficult to generalise the results to women with other underlying causes of CKD. Additionally, crude estimates were reported in this review without consideration for potential confounding factors.

Previous studies evaluating pregnancy outcomes in women with advanced stages of CKD have reported worse outcomes than those with earlier stages, although the results were inconsistent, and the magnitude of risk estimates differ across individual studies (9-11). These estimates are derived from small and single-centre cohorts, and we could not identify any systematic review of published data comparing risks for adverse pregnancy outcomes in women with advanced versus earlier stages of CKD. Moreover, associations between the cause of CKD and pregnancy outcomes are less studied: although the pregnancy outcomes are noted to be particularly poor

in certain women with lupus nephritis, the data for other forms of glomerular and non-glomerular kidney diseases are scant (12).

Thus, we conducted this systematic review and meta-analysis to synthesise the available published literature with respect to the associations between CKD and adverse pregnancy outcomes, and to evaluate, where possible, the extent to which the severity and cause of CKD modify these associations.

Methods

Protocol registration and reporting

The protocol for this systematic review was prospectively registered on the International Register of Systematic Reviews (identifier: CRD42020211925) (13). An additional question on CKD severity was added after registration. We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis checklist in the reporting of this systematic review (14).

Research Questions

1) Do pregnant women with CKD compared to pregnant women without CKD have a higher risk of adverse pregnancy outcomes?
2) Do pregnant women with late stages of CKD compared to early stages have a higher risk of adverse pregnancy outcomes?
3) Do specific causes of CKD associate with higher risks of adverse pregnancy outcomes?

Population, intervention, comparison, and outcome

The population, intervention, comparison, and outcome (PICO) approach specific to this systematic review and meta-analysis is detailed below:

Population of interest: All pregnant women

Intervention/exposure group: a) Pregnant women with CKD

b) Pregnant women with late stages of CKD

Comparison group: a) Pregnant women without CKD

b) Pregnant women with early stages of CKD

Outcomes: Primary (pre-eclampsia, CS, PTB [<37 weeks' gestation], and SGA). Secondary (maternal death, very preterm birth [VPTB, <34 weeks' gestation], LBW, neonatal intensive care unit [NICU] admission, stillbirth, neonatal death, and perinatal death).

Eligibility criteria

Observational studies (prospective cohort, retrospective cohort, or case-control designs) published in the English language were considered for inclusion if they met the PICO criteria. Reviews, case reports, editorial letters, expert opinions, and animal studies were not eligible for inclusion.

Information sources and search strategy

A systematic search of PubMed, Embase, and Web of Science was undertaken from the inception of the databases until November 12, 2020, using a detailed search strategy and key terms, including CKD and pregnancy outcomes. We also conducted a pre-submission updated search on May 24, 2021. The supplemental material (pages 2-4) provides the full search strategy that was used in each database. We additionally searched the bibliographies of previous systematic reviews of the same topic and searched the reference lists of all identified studies for further potentially relevant studies.

Study selection

Two reviewers (S.A and E.B) independently screened titles and abstracts, excluding studies that clearly did not meet the predefined inclusion criteria. Full texts of potentially eligible studies were obtained and screened independently by the same two reviewers, and where consensus could not be reached, a third reviewer was consulted. Where a duplicate publication of the same data (study population) existed, we only included the largest study. The process of study selection is outlined in **Figure 1**.

Data extraction and quality assessment

Three reviewers performed the data extraction (E.B, G.M, and S.A) independently using a standardised data extraction form. The following information was extracted: study author, year, country, study design, sample size, exposure and outcome definitions, statistical method used, reported effect measures (if not reported, we used raw data to calculate odds ratios [(ORs) and 95% confidence intervals (CI)], and factors adjusted for, if any.

Quality assessment of the included studies was performed independently by three reviewers (S.A, G.M, and E.B) using the Newcastle-Ottawa Scale. This scale uses a “star system”, in which stars are assigned to show higher quality on the basis of the following three criteria: selection of the study groups; comparability of the groups; and the ascertainment of the exposure and/or outcome of interest (the total score ranged from 0 to 9) (15). We considered

0–3 stars as low quality, 4–6 stars as moderate quality and 7–9 stars as high quality. Any discrepancies on screening, extraction and quality assessment were resolved through discussion and consensus involving the three reviewers (S.A, E.B, and G.M) and the lead investigator (A.K).

GRADE Certainty of the Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to evaluate the certainty of the evidence for primary outcomes by two reviewers independently (S.A and G.M). The certainty of the evidence was assessed using GRADEpro software based on the following domains: study design, risk of bias, imprecision, inconsistency, indirectness, and publication bias (16). Given the nature of the research questions specific to this systematic review (the exposure "CKD" is a medical condition), randomised control trials are not feasible. As a result, the certainty of the evidence for the included studies was assessed based on modifications of the traditional GRADE approach (17, 18). Thus, the included observational studies started as high quality and were downgraded accordingly based on the GRADE domains.

Statistical analysis

Random-effects meta-analyses using the generic inverse variance method were performed to calculate crude and adjusted pooled ORs of the associations between CKD and outcomes of interest. Forest plots were used to display crude and adjusted pooled ORs with 95% CIs. The risk difference (RD) estimates were calculated using GRADEpro, based on the event risk in the unexposed group, the pooled OR and 95% CI.

The statistical heterogeneity between studies was assessed using the I^2 statistics, and values ≥75% were considered high heterogeneity (19). Publication bias was evaluated using Egger's test and funnel plots. Subgroup analyses were performed according to the cause of CKD (glomerulonephritis, diabetic CKD, polycystic kidney disease (PKD) or unspecified CKD), study location (Asia, Australia, Europe, North America, or South America,) and the publication year (≤2010 or >2010). The subgroup meta-analysis calculates the effects within each subgroup level and then compares the pooled effect estimates for each subgroup. The *P*-value from the Cochran Q test—a test for interaction—was used to determine whether the magnitude of the effect of CKD differs according to causes of CKD, location, or year of publication. Studies with "zero" event in either group were excluded from analyses.

We also conducted a post-hoc analysis excluding a study that by design included women with CKD and superimposed acute kidney disease (4% had acute kidney disease) (20) to assess if that had an influence on the reported results. A statistically significant *P* value was based on a threshold of <0.05. All analyses were performed using Review Manager version 5.3, GRADEpro was used to estimate RDs, and Stata 16 for the Egger test.

Results

Search results and study characteristics

The initial search yielded 4,076 unique studies after the removal of duplicates (**Figure 1**). After screening the titles and abstracts, 143 full-text articles were reviewed. Of these, 113 articles not meeting inclusion criteria were excluded, leaving 30 articles for inclusion from this search. Reviewing reference lists of the included articles identified one additional article. A total of 31 unique articles were included in this review; 17 studies reported pregnancy outcomes in women with CKD vs those without (20-36), 10 studies reported results for early vs late stages of CKD (9-11, 37-43), and four studies reported results for both comparisons (44-47).

Of the 31 included cohort studies, the sample size ranged widely, from 12,524,119 participants in a population-based study (24) to 31 in a single-centre hospital-based study (41). The studies were published between 1988 and 2021. Eleven studies were conducted in Europe (11, 27, 29, 30, 32, 36, 40, 42, 44-46), ten in North America (9, 10, 20, 23-25, 31, 34, 35, 41), six in Asia (21, 22, 37-39, 43), two in Australia (33, 47), and two in South America (26, 28). Thirty studies reported definitions for CKD: nine defined CKD according to the National Kidney Foundation "Kidney Disease Outcomes Quality Initiative" guidelines (9, 21, 22, 25, 26, 38, 39, 46, 47), eleven used serum creatinine or proteinuria (11, 27-35, 41), six used eGFR (10, 37, 40, 42, 43, 45), four used medical coding (20, 23, 24, 36), and one study did not report the definition of CKD (44).

All studies scored between four and eight on the Newcastle-Ottawa Scale (**Supplemental Tables S1-S2**). The studies were rated as either moderate quality (n=16) or high quality (n=15); almost all studies with moderate quality did not adjust for confounding factors. More details about the characteristics of the studies, the definitions of CKD and outcomes from each included study are shown in (**Supplemental Tables S1-S2**). Additionally, forest plots of all analyses are provided in the **Supplement (Figures S1-S24)**.

Results of the Meta-analyses

The effect of CKD on adverse pregnancy outcomes (CKD compared to no CKD)

The summary results of all meta-analyses that investigated the association between CKD and adverse pregnancy outcomes are presented in **Table 1**. Of the 21 studies that compared adverse pregnancy outcomes in women with CKD vs those without, 14 studies had healthy women (general obstetric population) as the unexposed group. The remaining seven studies had women with other underlying medical conditions (diabetic in six studies (27, 29-33)), but with normal kidney function as the unexposed group (27, 29-34). Six studies reported adjusted effect estimates and that included demographic characteristics, such as maternal age, smoking, parity, body mass index and other comorbidities.

Fifteen studies reported effect estimates of pre-eclampsia: the crude pooled OR was 8.13 (95% CI, 4.41–15) (**Figure 2**), and the RD was 16% (95% CI, 8.4– 27). Four studies provided adjusted estimates for pre-eclampsia, which attenuated the OR to 2.58 (95% CI, 1.33–5.01) and RD to 4.1% (95% CI, 0.9–9.7). Ten studies reported effect estimates for CS: the pooled crude OR was 1.66 (95% CI, 1.34–2.06), and the RD was 6.4% (95% CI, 3.4–9.8). Three studies reported adjusted OR (aOR) for CS, and that showed similar results to the unadjusted estimate, aOR: 1.65 (95% CI, 1.21–2.25), and the RD was 6.3% (95% CI. 2.1–11.4). Fifteen studies reported effect estimates for PTB: the pooled crude OR was 3.07 (95% CI, 2.27–4.16) (**Figure 3**), and the RD was 9.2% (95% CI, 5.9–15.3). Four studies reported adjusted estimates for PTB, lowering the OR to 1.73 (95% CI, 1.31–2.27) and RD to 3.4% (95% CI, 1.5–5.8). Similarly, a higher risk of VPTB (<34 wk.) was observed in women with CKD from both crude estimates [ten studies, OR=4.85 (95% CI, 3.01–7.80), RD=3.1% (95% CI, 1.6–5.4)] and adjusted estimates [four studies, aOR: 2.18 (95% CI, 1.61–2.95), RD=1% (95% CI, 0.5–1.6)].

Ten studies reported effect estimates for SGA: the crude OR was 2.69 (95% CI, 1.70–4.24), RD=4% (95% CI, 1.7–7.5), and the aOR (three studies) was 1.93 (95% CI, 1.06–3.52), RD=2.3% (95% CI, 0.1–5.9). Few studies reported effect estimates for miscarriage, stillbirth, and perinatal death, and both adjusted and unadjusted results were non–significant (**Table 1**). Additionally, the combined outcome of pregnancy loss showed an insignificant association with CKD [four studies, pooled aOR: 1.58 (95% CI, 0.92–2.73), RD=0.2% (95% CI, 0.0–0.7].

Assessment of heterogeneity and publication bias

Heterogeneity between studies was low for perinatal death (I^2=0%), moderate for CS (I^2=56%), and high for other outcomes. Although heterogeneity was high for most outcomes in this

comparison, most effect estimates of studies examining the effect of pre-eclampsia and PTB (**Figures 1** & **2**) are in the same direction suggesting an association with CKD, which may indicate that heterogeneity between studies was because of poor overlapping between studies' 95% CIs (48). This was also explored more in subgroup analyses based on the cause of CKD, study location and year of publication. For publication bias, funnel plots of pre-eclampsia (**Figure S1**), CS (**Figure S2**), PTB (**Figure S3**), VPTB (**Figure S4c**) and SGA (**Figure S5**) show approximately symmetric distributions, and the results of the Egger test were nonsignificant for all outcomes (*P*-values=0.38; 0.47; 0.17; 0.10; and 0.44 respectively), indicating that publication bias was unlikely to be a substantial problem.

The effect of CKD severity on adverse pregnancy outcomes (advanced stages compared to early stages of CKD)

A summary of the results of the included studies that report adverse pregnancy outcomes based on the severity of kidney disease are available in **Table 1**. Of the 14 studies, eight compared the outcomes in women with earlier stage (stages 1 or 1-2) CKD vs later stage (stages 2-5 or 3-5) CKD (9, 37-39, 45-47). Four studies included women with stages 1-3 vs 4-5 (10, 40, 42, 43). One study defined CKD severity using creatinine level (<125 vs >125 umol/L) (11), and another study defined the severity of kidney disease according to urine protein level (41), whereas one study did not report the CKD definition (44). Only three studies in this comparison adjusted for potential confounders, all of them adjusted for proteinuria, and two of these adjusted for hypertension as well.

The results suggest that later stages of CKD, compared to earlier stages, were associated with higher odds of pre-eclampsia [10 studies; crude OR=2.77 (95% CI, 1.73–4.44), RD=24% (95% CI, 12–35)], CS [10 studies; crude OR=1.53 (95% CI, 1.02–2.30), RD=10% (95% CI, 0.5–19)], PTB [12 studies; crude OR=4.21 (95% CI, 2.99–5.92), RD=34% (95% CI, 26.4–42)], and VPTB [eight studies; crude OR=3.11 (95% CI, 2.06–4.69), RD=19% (95% CI, 11–29)]. Eleven studies showed an association between CKD severity and SGA [crude OR=2.43 (95% CI, 1.33–4.46), RD=18% (95% CI, 5.2–33)], but this association was no longer statistically significant after adjustment for proteinuria and hypertension [three studies, aOR: 2.42 (95% CI, 0.82–7.15), RD=17% (95% CI, –2.8–43)].

The risks of LBW [three studies; crude OR=3.17 (95% CI, 1.05–9.62), RD=22% (95% CI, 0.7–49)] and NICU admission [three studies; crude OR=2.94 (95% CI, 1.05–9.62.08), RD=26% (95% CI, 11–39)] were higher in women with advanced stages of CKD. We also observed a

higher risk of stillbirth, neonatal death, and perinatal death in later stages of CKD compared to earlier stages (**Table 1**). The combined outcome of pregnancy loss also supported a higher risk in women with advanced stages of CKD [9 studies; crude OR=4.39 (95% CI, 2.40–8.02), RD=13% (95% CI, 6–24)]. Few studies reported adjusted effect estimates (adjusted for proteinuria and hypertension), and these reported a significant risk of pre-eclampsia (n=1) and VPTB (n=2) (**Table 1**).

Assessment of heterogeneity and publication bias

Heterogeneity among studies was low in studies that assessed the outcomes including stillbirth, neonatal death, perinatal death, pregnancy loss, PTB, VPTB, NICU admission (I^2=0%) and CS (I^2=21%). A moderate level of heterogeneity was observed between studies examining the effect of pre-eclampsia (I^2=31%), LBW (I^2=58%) and SGA (I^2=59% and 56% in the adjusted model). This level of moderate heterogeneity might be due to poor overlapping of 95% CIs for effect estimates of individual studies. The tests for funnel asymmetry were nonsignificant for pre-eclampsia (*P*=0.14), CS (*P*=0.50), and SGA (*P*=0.61), suggesting that publication bias is not a concern (**Supplemental Figures S9b**; **S10b**; and **S13c**, respectively). However, there was little evidence for small-study effects for PTB (*P*=0.032, **Supplemental Figure S11b**).

The effect of the cause of CKD on adverse pregnancy outcomes

When we investigated risks based on the cause of CKD, we determined that all causes were associated with a higher risk of pre-eclampsia, PTB, and SGA (**Table 2** & **Figures S19**, **S11** & **S13**). Adjustment for confounding factors in this analysis refers mainly to maternal demographic characteristics and other comorbidities.

The magnitude of risk of pre-eclampsia appears higher in women with glomerulonephritis and diabetic CKD [crude OR=6.52 (95% CI, 2.02–21.1), and 9.19 (95% CI, 6.05–14.0), respectively] than in women with PKD [OR=4.36 (95% CI, 3.32–5.71)]. However, adjusted estimates showed similar risks across different subgroups [glomerulonephritis: aOR=2.13 (95% CI, 1.84–2.47); diabetic CKD: aOR=2.80 (95% CI, 1.55–5.05); and PKD: aOR=3.98 (95% CI, 2.98–5.32)]. Women with diabetic CKD were more likely to have PTB [crude OR=4.71 (95% CI, 1.46–15.2), aOR=4.76 (3.65–6.21] and CS [crude OR=3.08 (95% CI, 0.71–13.30), aOR=3.75 (95% CI, 2.76–5.10)] than other CKD groups. There was effect modification by cause of CKD, which suggested that different CKD causes had differing risks of pre-eclampsia (*P*=0.03), VPTB (*P*<0.00001) and SGA (*P*=0.008). In addition, one study reported

the effect estimate for women with renovascular CKD, compared to normotensive women without CKD, which suggested a higher odds of pre-eclampsia [aOR=3.64 (95% CI, 2.18–6.09)], indicated PTB [aOR=8.09 (95% CI, 5.73–11.4)], and SGA [aOR:=328 (95% CI, 2.06–5.20)] (36).

Heterogeneity was moderate to high for all meta-analyses, and that was explained by causes of CKD, particularly for VPTB and SGA (**Supplemental Figures S22** & **S23**). When this was further investigated, a high level of heterogeneity for PTB in the diabetic CKD subgroup (n=6, I^2=96%) was owing to two studies with outlying effect estimates (27, 36). When these studies were excluded, the pooled crude OR for PTB in this subgroup was changed to 4.18 (95% CI, 2.86–6.11; I^2= 0%). Similarly, excluding these studies from the pre-eclampsia analysis decreased heterogeneity. The explanation for outlier results in these studies might be explained by studies inclusion criteria, as one study included women with microalbuminuria without reduced eGFR (27), whereas the other study compared outcomes to the general obstetric population and not mainly diabetic women without CKD (36), which was used as the reference group in other studies examining the risk of pregnancy outcomes in women with diabetic CKD.

Sensitivity analyses by study location and year of publication

The results of subgroup analyses by publication year (≤2010 vs >2010) showed a significant decreased risk over time for CS (*P*=0.02) and SGA (*P*<0.0001) and also explained some of the heterogeneity among the studies (**Supplemental Table S3**). However, no differences were found by study location (**Supplemental Table S3**).

GRADE Certainty of the Evidence

Considering that our review included observational studies, the certainty of the evidence was judged to be “low” for pre-eclampsia, PTB and VPTB, and “very low” for SGA and CS. Therefore, the certainty of the evidence overall across all outcomes was judged to be very low. The evidence was downgraded (depending on the outcome of interest) due to a serious risk of bias in the included studies (studies included were observational, most studies reported crude estimates and confounding was judged to be a serious concern); serious imprecision (the included studies had very wide 95% CIs); and inconsistency (due to a moderate level of heterogeneity that was not explained by subgroup analyses, as well as effect estimates in varying directions and crossing the line of no effect). Details about the GRADE evaluation are provided in **Table 3**.

Discussion

This systematic review and meta-analysis of 31 international studies over the last four decades examined associations between pre-pregnancy CKD and risk of adverse pregnancy outcomes. We identified three main findings. First, we confirmed that CKD is a strong risk factor for adverse pregnancy outcomes. For example, the odds for pre-eclampsia were 8-fold higher in women with CKD compared to women without CKD and remained approximately 3-fold higher after adjusting for factors including maternal age, smoking, body mass index, parity, and other comorbidities. Second, we confirmed that later stages of CKD are associated with greater risk than earlier stages, supporting findings from individual studies that have not been evaluated in a contemporary meta-analysis. Finally, we determined that the risk associated with CKD differs depending on the cause of CKD: specifically, risks were higher amongst women with diabetic CKD, particularly for CS, PTB, and SGA.

Our review reinforces previous findings on the occurrence of adverse pregnancy outcomes in women with CKD, compared to those without CKD, by including more studies from different settings (7, 8). In contrast to the previous reviews (7, 8), we considered the cause of CKD when adverse pregnancy outcomes were compared between women with and without CKD. We also investigated the risk of adverse pregnancy outcomes among pregnant women with late stages of CKD compared to early stages. Additionally, a previous review reported high quality of the evidence for pre-eclampsia and PTB and low for SGA/LBW (8), but our GRADE evaluation showed low and very low quality of evidence for these outcomes, respectively.

There is limited research on the risk of adverse pregnancy outcomes among women with specific types of kidney diseases. In our review, most studies (n=19) combined a variety of kidney disease aetiologies in their analyses when examining the risk of adverse pregnancy outcomes. Of these, 14 reported percentages of specific diagnoses, and glomerulonephritis was the most common diagnosis in pregnant women (9, 10, 36, 38-40, 42-44, 47). Proteinuria has been found to be an important predictor of outcome in immunoglobulin A(IgA) nephropathy, which is the most common primary glomerulonephritis in pregnant women (12).

The available literature suggests that proteinuria (42, 49) and chronic hypertension (36, 42, 49) are strong determinants of adverse pregnancy outcomes in women with CKD. However, an Italian cohort study aimed to investigate whether adverse pregnancy outcomes in women with stage 1 CKD were due to hypertension, proteinuria, presence of systemic disease, or other factors associated with CKD and indicated that any persistent kidney damage (even with

preserved kidney function) in the absence of hypertension, significant proteinuria or systemic disease, was associated with a higher risk for adverse pregnancy outcomes (49). Our findings from the subgroup analysis, including studies that specified the CKD subtypes, suggested a higher risk of adverse pregnancy outcomes in pregnant women with glomerulonephritis. Furthermore, we found that pregnancies in women with diabetic CKD had poor pregnancy outcomes, particularly for preeclampsia, CS and SGA, and the magnitude of effect estimates varies among included studies based on albuminuria level (microalbuminuria/macroalbuminuria). The pregnancy outcomes among pregnant women with PKD were reported in two studies, and they showed an association with pre-eclampsia, CS, PTB, SGA and stillbirth. We did not include pregnant women with lupus nephritis in our review as this particular group was studied in a recent meta-analysis that reported an association between lupus nephritis and pre-eclampsia (OR=2.84), PTB (OR=1.92), and fetal growth restriction (OR=1.43) (50).

Overall, the finding of associations between adverse pregnancy outcomes and different CKD causes confirms previous research (51). However, direct comparisons of pregnancy outcomes between women with a specific cause of CKD vs a comparator cause of CKD are lacking.

Strengths and Limitations

The strengths of this meta-analysis include the development and use of a comprehensive search strategy, a prospectively registered protocol, the additional comparison of pregnancy outcomes across CKD stages, subgroup analyses by cause of CKD, and inclusion of studies from multiple geographic regions spanning four decades. In addition, each process of the systematic review was carried out by at least two independent reviewers using standardised data extraction forms and validated quality appraisal tools. However, several limitations should be noted. The review was limited to English language studies only, and the grey literature was not searched. Although we estimated the crude and adjusted estimates that highlighted significant confounding when comparing the crude and adjusted estimates, most of the included studies reported crude estimates only, were performed in a single centre and were of small sample size. Nevertheless, by pooling the results of these individual studies, we aimed to better estimate the true magnitude of risk. Confounding factors were addressed in nine studies only (9, 20, 24, 25, 27, 35, 36, 42, 46), and that may attenuate the reported estimates between CKD and adverse pregnancy outcomes. Therefore, future studies should be designed to account for potential confounding to improve our understanding of these associations and the role of potential confounding.

These studies were also susceptible to other limitations of observational research, and the overall certainty of the evidence across all outcomes was judged to be "very low" using the GRADE approach (certainty was downgraded due to concerns regarding bias [incomplete adjustment for confounding] and imprecision [most studies of small sample size with very wide CIs)] and inconsistency. We cannot eliminate the possibility of under- or over- diagnosis of pre-eclampsia in some women with CKD, who had hypertension and/or proteinuria before pregnancy. Further, CKD definitions varied across the included studies, including the threshold at which a patient was considered to have early vs late CKD. Finally, we lacked sufficient data on proteinuria and blood pressure control before and during pregnancy, which are known to be strong risk factors for adverse pregnancy outcomes in women with CKD (49). Accordingly, we could not determine whether associations with the cause of CKD were mediated by these (potentially modifiable) factors. Additionally, data on pre-eclampsia were not detailed enough to investigate whether the magnitude of risk associated with CKD varied by pre-eclampsia severity (severe vs mild or term vs preterm). Similarly, data on CS were reported as overall deliveries in most studies without distinguishing between elective or emergency CS.

Women with CKD are considered a high-risk group during pregnancy and should be offered preconception counselling by a multidisciplinary team, with close monitoring during pregnancy, delivery and in the postnatal period. However, not all women with CKD are the same. By quantifying risk differences depending on severity and cause of CKD, this systematic review will enable clinicians to better tailor care and counselling to individual patient risk. Future studies examining associations between CKD and adverse pregnancy outcomes need to account not only for the severity of CKD but also for the cause of CKD and factors (proteinuria, hypertension, immunosuppressive therapies, disease activity) that might mediate this risk.

Conclusions

The results of this meta-analysis confirmed an association between pre-pregnancy CKD and adverse pregnancy outcomes, with different risks according to the cause and the severity of CKD. We hope that these findings might support clinicians aiming to counsel women with CKD considering pregnancy. However, we acknowledge that most of the included observational studies had significant limitations, which highlights the need for more robust research in the future. In particular, we advocate for the development of an international pregnancy registry of women with CKD, which would comprehensively characterise women with CKD in early pregnancy and prospectively collect data on a core set of standardised

pregnancy outcomes. Such an initiative would accurately quantify absolute risks, and identify risk factors, for adverse pregnancy outcomes in women with CKD, enabling pregnancy counselling to be better tailored to individual patient risk and generating hypotheses to be tested in future interventional studies.

Conflict of Interest: The authors report no conflict of interest.

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Table 1. Summary results of meta-analyses of pregnancy outcomes in women with chronic kidney disease

Maternal/fetal outcome	*Crude estimates*					*Adjusted Estimates*				
	No. of studies	No. of participants	Pooled OR (95% CI)	RD (95% CI)	I^2, %	No. of studies	No. of participants	Pooled OR (95% CI)[a]	RD (95% CI)	I^2, %
Women with CKD compared to women without CKD										
Pre-eclampsia	15	2,782,133	8.13 [4.41, 15]	16% [8.4, 27]	93	4	2,777,209	2.58 [1.33, 5.01]	4.1% [0.9, 9.7]	93
Caesarean section	10	2,780,815	1.66 [1.34, 2.06]	6.4% [3.4, 9.8]	56	3	2,776,363	1.65 [1.21, 2.25]	6.3% [2.1, 11.4]	84
Maternal death	–	–	–	–	–	1	1,556	1.13 [0.44, 2.92]	0.1% [–0.6, 1.9]	–
Preterm birth (<37 wk.)	15	2,837,905	3.07 [2.27, 4.16]	9.2% [5.9, 13.3]	92	4	2,831,929	1.73 [1.31, 2.27]	3.4% [1.5, 5.8]	92
Very preterm birth (<34 wk.)	10	2,833,576	4.85 [3.01, 7.80]	3.1% [1.6, 5.4]	87	4	2,832,177	2.18 [1.61, 2.95]	1.0% [0.5, 1.6]	65
Small for gestational age	10	2,780,942	2.69 [1.70, 4.24]	4.0% [1.7, 7.5]	78	3	2,776,363	1.93 [1.06, 3.52]	2.3% [0.1, 5.9]	89
Low birthweight	1	43	4.00 [0.80, 20.1]	24% [–2.2, 62]	–	1	1,556	2.38 [1.64, 3.44]	7.2% [3.5, 12]	–
Neonatal intensive unit admission	1	144	2.40 [1.40, 4.11]	-	–	1	1,556	1.80 [1.22, 2.66]	4.0% [1.1, 7.9]	–
Miscarriage	3	809	2.71 [0.76, 9.62]	11% [–1.8, 37]	75	–	–	–	–	–
Stillbirth	3	15,354,062	2.47 [0.72, 8.47]	0.6% [–0.1, 2.8]	99	3	15,354,062	1.67 [0.96, 2.92]	0.3% [0.0, 0.7]	94
Perinatal death	2	422	4.07 [1.02, 16.2]	4.3% [0, 18]	0	1	1,556	0.50 [0.05, 5.53]	–0.1% [–0.2, 1.1]	–

Pregnancy loss[b]	8	15,355,293	2.74 [1.22, 6.16]	0.7% [0.1, 2.0]	96	4	15,355,618	1.58 [0.92, 2.73]	0.2% [0, 0.7]	91
Late stages compared to early stages of CKD										
Pre-eclampsia	10	833	2.77 [1.73, 4.44]	24% [12, 35] [b]	31	1	126	4.50 [1.29, 15.7]	35% [4.9, 59]	–
Cesarean section	10	811	1.53 [1.02, 2.30]	10% [0.5, 19]	21	–	–	–	–	–
Preterm birth (<37 wk.)	12	1,279	4.21 [2.99, 5.92]	34% [26.4, 42] [b]	0	1	126	2.03 [0.89, 4.63]	17% [–2.5, 37]	–
Very preterm birth (<34 wk.)	8	716	3.11 [2.06, 4.69]	19% [11, 29] [b]	0	2	207	3.10 [1.38, 6.95]	18% [4, 38]	0
Small for gestational age	11	729	2.43 [1.33, 4.46]	18% [5.2, 33]	59	3	301	2.42 [0.82, 7.15]	17% [–2.8, 43]	56
Low birthweight	3	323	3.17 [1.05, 9.62]	22% [0.7, 49]	58	–	–	–	–	–
Neonatal intensive unit admission	3	233	2.94 [1.65, 5.24]	26% [11, 39] [b]	0	–	–	–	–	–
Miscarriage	1	35	1.33 [0.19, 9.31]	3.6% [–10.3, 45]	–	–	–	–	–	–
Stillbirth	5	279	3.10 [1.32, 7.29]	12% [2, 28]	0	–	–	–	–	–
Neonatal death	3	223	6.74 [2.54, 17.9]	22% [6.9, 43]		1	81	2.90 [0.10, 84]	8.4% [–4.6, 77]	–
Perinatal death	3	360	5.81 [2.27, 14.9]	12% [3.6, 29]	0	–	–	–	–	–
Pregnancy loss[c]	9	654	4.39 [2.40, 8.02]	13% [6, 24] [b]	0	1	81	2.90 [0.10, 84]	8.4% [–4.6, 77]	–

CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; RD, risk difference. [a] For adjusted estimates, we followed the author's definition: a study comparing adverse outcomes in CKD vs no CKD adjusted for factors including maternal age, smoking, body mass index, race, income, educational level, parity, and other comorbidities. Whereas the three studies comparing early vs late stages CKD adjusted for proteinuria and two of them adjusted for hypertension. [b] One study (Seah, 2020) did not report the number of events in each group for these outcomes; therefore, it was not added to the study event rates; [c] pregnancy loss included miscarriage, stillbirth, neonatal death and/or perinatal death effect estimates.

Table 2. Summary results of meta-analyses of adverse pregnancy outcomes in women with CKD compared to women without CKD, according to the cause of CKD

Maternal/fetal outcome	*Crude estimates*					*Adjusted Estimates*				
	No. of studies	No. of participants	Pooled OR (95% CI)	RD (95% CI)	I^2, %	No. of studies	No. of participants	Pooled OR (95% CI)[a]	RD (95% CI)	I^2, %
Pre-eclampsia										
Glomerulonephritis CKD	4	2,758,078	6.52 [2.02, 21.1]	13% [2.7, 34]	88	1	2,756,102	2.13 [1.84, 2.47]	2.9% [2.2, 3.8]	–
Diabetic CKD	7	2,753,496	9.19 [6.05, 14.0]	18% [12, 26][b]	57	2	2,752,847	2.80 [1.55, 5.05]	4.6% [1.5, 9.8]	67
PKD	2	2,752,680	4.36 [3.32, 5.71]	8.3 [5.9, 11]	0	1	2,752,269	3.98 [2.98, 5.32]	7.4% [5, 10]	–
Unspecified CKD	5	2,778,417	5.30 [2.02, 13.9]	19% [5.5., 42]	95	3	2,776,363	2.27 [1.06, 4.87]	3.3% [0.2, 9.5]	94
Caesarean section										
Glomerulonephritis CKD	3	2,758,033	1.45 [1.15, 1.85]	4.5% [1.5, 8.1]	45	1	2,756,102	1.52 [1.38, 1.67]	5.1% [3.8, 6.5]	–
Diabetic CKD	4	2,752,369	3.08 [0.71, 13.3]	17% [–3.1, 52]	93	1	2,752,001	3.75 [2.76, 5.10]	22% [15, 29]	–
PKD	2	2,752,680	1.97 [1.03, 3.77]	9.1% [0.3, 22]	72	1	2,751,735	2.67 [2.14, 3.33]	15% [11, 19]	–
Unspecified CKD	4	2,778,105	1.98 [1.37, 2.86]	9.2%. [3.7, 16]	81	3	2,776,363	1.65 [1.21, 2.25]	6.3% [2.1, 11]	84
Preterm birth <37 wk.										
Glomerulonephritis CKD	4	2.758,147	5.98 [2.20, 16.3]	19% [5.5, 42]	95	1	2,756,102	2.20 [1.98, 2.44]	5.5% [4.5, 6.5]	–
Diabetic CKD	6	2,753,510	4.71 [1.46, 15.2]	17% [2.5, 43][b]	96	1	2,752,001	4.76 [3.65, 6.21]	15% [11, 20]	–
PKD	2	2,752,680	2.12 [1.04, 4.30]	5.1% [0.2, 14]	71	1	2,752,269	2.55 [1.94, 3.35]	7% [4.4, 10]	–
Unspecified CKD	6	2,834,297	2.17 [1.62, 2.90]	5.4% [2.9, 8.5]	90	4	2,776.286	1.73 [1.31, 2.27]	3.4% [1.5, 5.8]	92
Very preterm birth <34 wk.										

Glomerulonephritis CKD	2	1,931	19.2 [10.4, 35.5]	15% [8.4, 25]	0	–	–	–	–	–
Diabetic CKD	5	1,558	4.28 [2.45, 7.47]	16% [7.6, 26][b]	50	1	846	1.60 [0.64, 4.00]	3.2% [–2, 1.4]	–
PKD	–	–	–	–	–	–	–	–	–	–
Unspecified CKD	3	2,830,087	2.15 [1.67, 2.76]	0.9% [0.6, 1.4]	53	3	2,831,885	2.28 [1.62, 3.21]	1.1% [0.5, 1.8]	76
Small for gestational age										
Glomerulonephritis CKD	2	2,757,646	1.77 [1.52, 2.07]	1.9% [1.3, 2.6]	0	1	2,756,102	1.54 [1.31, 1.81]	1.3% [0.8, 2]	–
Diabetic CKD	4	2,752,560	5.14 [2.52, 10.5]	9.3% [3.6, 19]	45	1	2,752,001	4.50 [2.92, 6.94]	8% [4.6, 13]	–
PKD	2	2,752,680	2.59 [1.84, 3.64]	3.8% [2, 6.1]	0	1	2,752,269	2.45 [1.66, 3.62]	3.5% [1.5, 6.1]	–
Unspecified CKD	5	2,778,428	2.49 [1.34, 4.61]	3.6%. [0.8, 8.2]	84	3	2,776,363	1.93 [1.06, 3.52]	2.3% [0.1, 5.9]	89
Low birthweight										
Glomerulonephritis CKD	–	–	–	–	–	–	–	–	–	–
Diabetic CKD	1	43	4.00 [0.80, 20.1]	24% [–2.2, 62]	–	–	–	–	–	–
PKD	–	–	–	–	–	–	–	–	–	–
Unspecified CKD	–	–	–	–	–	1	1,556	2.38 [1.64, 3.44]	7.2% [3.5, 12]	–
Neonatal intensive unit admission										
Glomerulonephritis CKD	–	–	–	–	–	–	–	–	–	–
Diabetic CKD	1	144	2.40 [1.40, 4.11]	-[b]	–	–	–	–	–	–
PKD	–	–	–	–	–	–	–	–	–	–
Unspecified CKD	–	–	–	–	–	1	1,556	1.80 [1.22, 2.66]	4% [1.1, 7.9]	–
Stillbirth										

Glomerulonephritis CKD	1	2,756,102	1.31 [0.82, 2.09]	0.1% [–0.1, 0.4]	–	1	2,756,102	1.12 [0.70, 1.79]	0.0% [–0.1, 0.3]	–
Diabetic CKD	1	2,752,001	5.75 [2.40, 13.8]	1.5% [0.5, 4.1]	–	1	2,752,001	1.55 [0.64, 3.75]	0.2% [–0.1, 0.9]	–
PKD	1	2,752,269	2.84 [1.18, 6.84]	0.6% [0.1, 1.9]	–	1	2,752,269	2.73 [1.13, 6.60]	0.6% [0, 1.8]	–
Unspecified CKD	3	15,354,062	2.47 [0.72, 8.47]	0.6% [–0.1, 2.8]	99	3	15,354,062	1.67 [0.96, 2.92]	0.3% [0, 1.8]	94
Perinatal death										
Glomerulonephritis CKD	–	–	–	–	–	–	–	–	–	–
Diabetic CKD	2	422	4.07 [1.02, 16.2]	4.3% [0, 18]	0	–	–	–	–	–
PKD	–	–	–	–	–	–	–	–	–	–
Unspecified CKD	–	–	–	–	–	1	1,556	0.50 [0.05, 5.53]	–0.1% [–0.2, 1.1]	–

CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; PKD, polycystic kidney disease; RD, risk difference. [a] For adjusted estimates, we followed the author's definition: these studies adjusted for factors including maternal age, smoking, body mass index, race, income, educational level, parity, and other comorbidities. [b] One study (Seah, 2020) did not report the number of events in each group for these outcomes; therefore, it was not added to the study event rates.

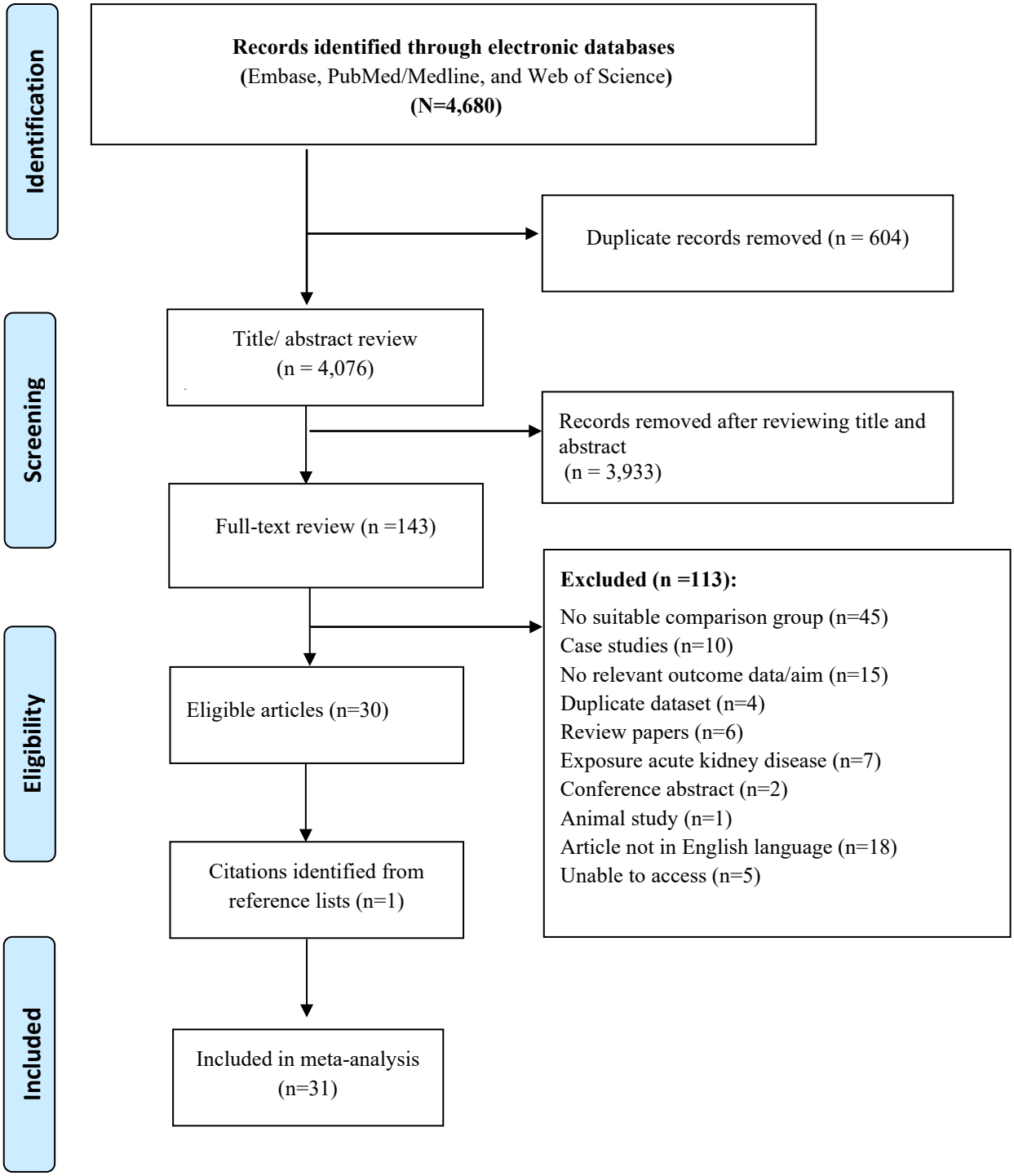
Table 3. Certainty of the evidence assessed using the GRADE approach for chronic kidney disease and adverse pregnancy outcomes

Outcome	№ of studies	Certainty assessment					Summary of findings				
							Study event rates (%)		*Relative effect (95% CI)*[a]	*Anticipated absolute effects*	
		Risk of bias	Inconsistency	Indirectness	Imprecision	Overall certainty of evidence	No CKD	CKD		Risk with no CKD	Risk difference with CKD
Pre-eclampsia[b]	16	Serious[c]	Not serious	Not serious	Serious[d]	⨁⨁◯◯ LOW	76290/2759512 (2.8%)	1299/24033 (5.4%)	**OR** 6.79 (3.93, 11.8)	28 per 1,000	**134 more per 1,000** (from 73 more to 222 more)
Preterm birth[b]	16	Serious[c]	Not serious[e]	Not serious	Serious[d]	⨁⨁◯◯ LOW	145725/2812368 (5.2%)	2612/26949 (9.7%)	**OR 2.88** (2.16, 3.83)	52 per 1,000	**84 more per 1,000** (from 54 more to 121 more)
Small for gestational age	11	Serious[c]	Serious[f]	Not serious	Serious[d]	⨁◯◯◯ VERY LOW	70589/2758432 (2.6%)	929/23966 (3.9%)	**OR 2.36** (1.61, 3.47)	26 per 1,000	**33 more per 1,000** (from 15 more to 58 more)
Caesarean section	11	Serious[c]	Serious[g]	Not serious	Serious[d]	⨁◯◯◯ VERY LOW	327224/2758410 (11.9%)	4460/23961 (18.6%)	**OR 1.58** (1.32, 1.88)	119 per 1,000	**57 more per 1,000** (from 32 more to 83 more)
Very Preterm birth[b]	11	Serious[c]	Not serious	Not serious	Serious[d]	⨁⨁◯◯ LOW	23648/2808571 (0.8%)	708/26417 (2.7%)	**OR 4.70** (2.92, 7.57)	8 per 1,000	**30 more per 1,000** (from 16 more to 52 more)

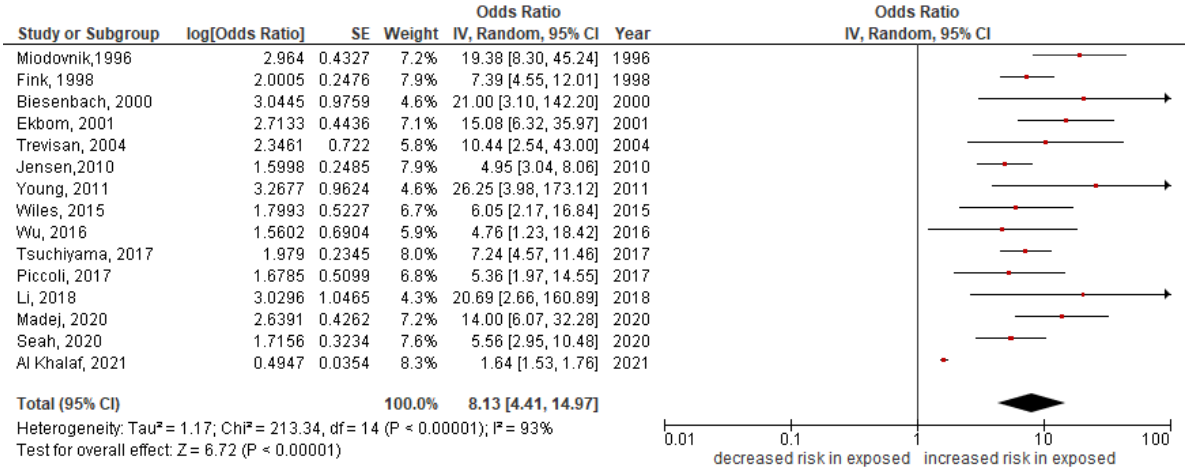
Explanations

[a] Pooled odds ratios presented are a combination of adjusted (when reported by included studies) and crude effect estimates; [b] One study (Seah, 2020) did not report the number of events in each group for these outcomes; therefore, it was not added to the study event rates. Contact with the author proved for this information proved unsuccessful; [c] Downgraded one level for risk of bias (included studies were observational, few studies reported adjusted effect estimates and confounding was judged to be a serious concern); [d] Downgraded one level for imprecision (included studies had very wide 95% confidence intervals); [e] Although heterogeneity levels between studies was high (I^2=92), almost all estimates from forest plots consistently supported associations in the same direction; [f] Downgraded one level for inconsistency (due to a moderate level of heterogeneity that was not explained by subgroup analysis, as well as effect estimates in varying directions and crossing the line of no effect); [g] Downgraded one level for inconsistency (due to varying directions of effect estimates and some estimates crossing the line of no effect. Although heterogeneity was high, but that was mainly due to different causes of CKD)

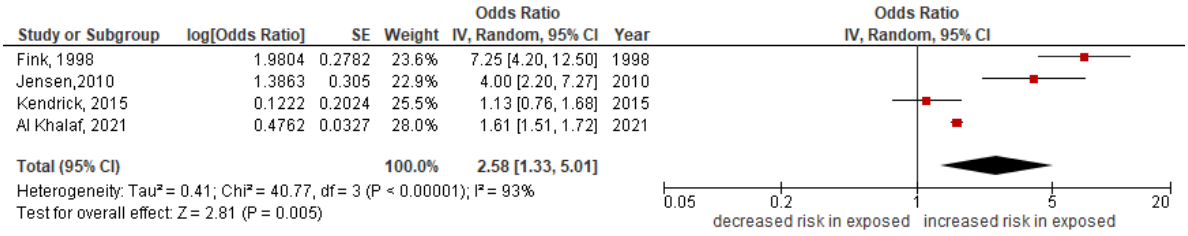
Figure 1. PRISMA flow diagram of studies on the association between chronic kidney disease and adverse pregnancy outcome



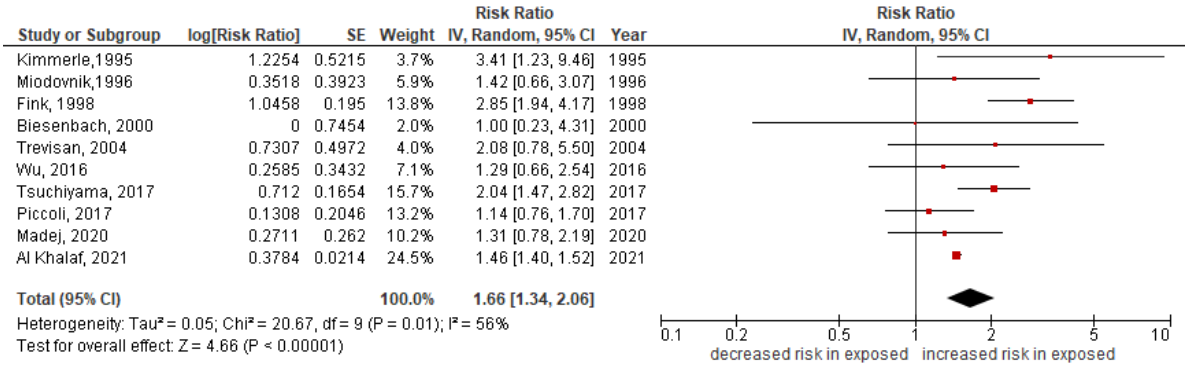
A **Pre-eclampsia** (crude estimates)



B **Pre-eclampsia** (adjusted estimates)



C **Caserean section** (crude estimates)



D **Caserean section** (adjusted estimates)

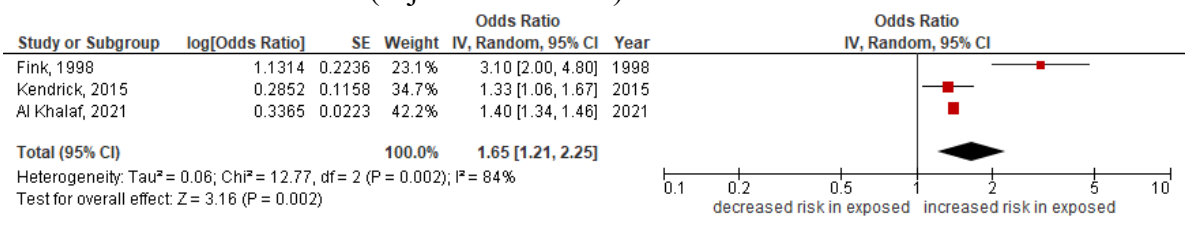
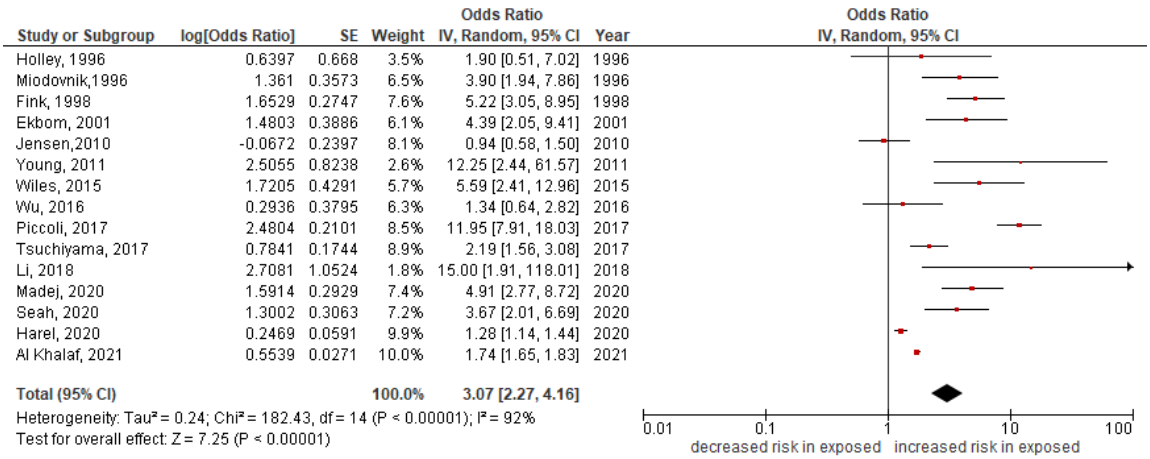
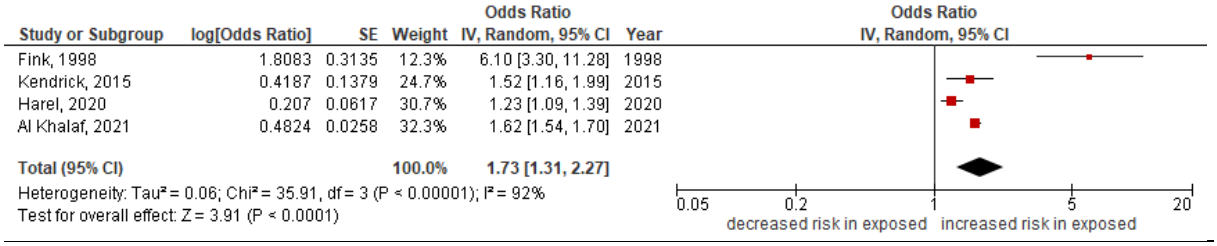


Figure 2. Forest plots of studies of the association between chronic kidney disease and maternal complications

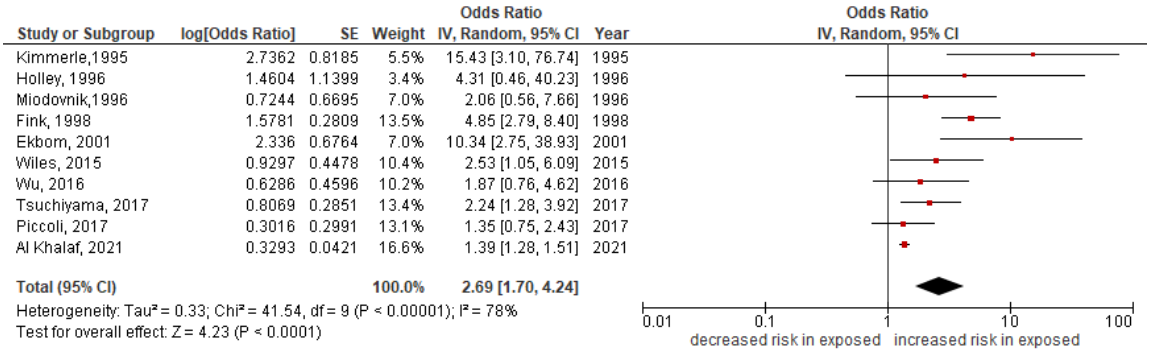
A **Preterm birth (<37 wk.)** (crude estimates)



B **Preterm birth (<37 wk.)** (adjusted estimates)



C **Small for gestational age** (crude estimates)



D **Small for gestational age** (adjusted estimates)

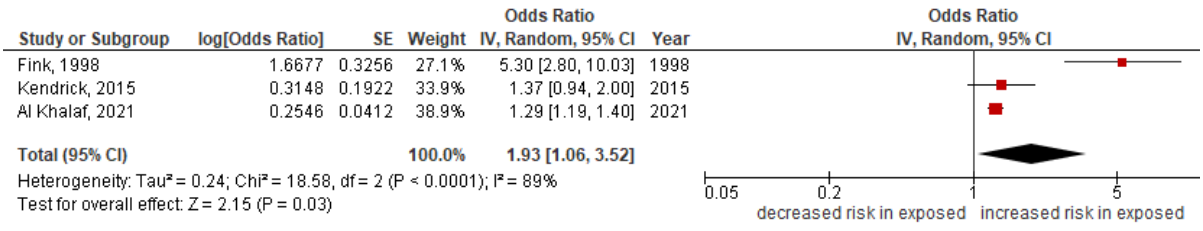


Figure 3. Forest plots of studies of the association between chronic kidney disease and fetal/neonatal outcomes

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