Chronic kidney disease and adverse pregnancy outcomes: a systematic review and meta-analysis

Sukainah Al Khalaf, MPH; Elizabeth Bodunde, MPH; Gillian M. Maher, PhD; Éilis J. O'Reilly, ScD; Fergus P. McCarthy, PhD; Michelle M. O'Shaughnessy, MB BCh, MS, MD; Sinéad M. O'Neill, PhD; Ali S. Khashan, PhD

OBJECTIVE: Limited evidence exists on the role that the cause of chronic kidney disease plays in determining pregnancy outcomes. The aim of this systematic review and meta-analysis was to examine the association between chronic kidney disease and adverse pregnancy outcomes by the cause and severity of chronic kidney disease where reported. The protocol was registered under the International Prospective Register of Systematic Reviews (CRD42020211925).

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 the pregnancy outcomes in women with or without chronic kidney disease were included. Two reviewers independently screened titles, abstracts, and full-text articles according to a priori defined inclusion criteria.

METHODS: Data extraction and quality appraisal were performed independently by 3 reviewers. The grading of recommendations, assessment, development, and evaluation approach was used to assess the overall certainty of the evidence. Random-effects meta-analyses were used to calculate the pooled estimates using the generic inverse variance method. The primary outcomes included preeclampsia, cesarean delivery, preterm birth (<37 weeks' gestation), and small for gestational age babies.

RESULTS: Of 4076 citations, 31 studies were included. Prepregnancy chronic kidney disease was significantly associated with a higher odds of preeclampsia (pooled crude odds ratio, 8.13; [95% confidence interval, 4.41−15], and adjusted odds ratio, 2.58; [1.33−5.01]), cesarean delivery (adjusted odds ratio, 1.65; [1.21−2.25]), preterm birth (adjusted odds ratio, 1.73; [1.31−2.27]), and small for gestational age babies (adjusted odds ratio, 1.93; [1.06−3.52]). The association with stillbirth was not statistically significant (adjusted odds ratio, 1.67; [0.96−2.92]). Subgroup analyses indicated that different causes of chronic kidney disease might confer different risks and that the severity of chronic kidney disease is associated with a risk of adverse pregnancy outcomes, as pregnancies with later stages of chronic kidney disease had higher odds of preeclampsia, preterm birth, and small for gestational age babies than those at earlier stages. The grading of recommendations, assessment, development, and evaluation certainty of the evidence overall was "very low".

CONCLUSION: This meta-analysis quantified the associations between prepregnancy chronic kidney disease and adverse pregnancy outcomes, both overall and according to the cause and severity of the disease. These findings might support the clinicians aiming to counsel women having chronic kidney disease by allowing them to tailor their advice according to cause and severity of the chronic kidney disease. We identified the gaps in the literature, and further studies examining the effect of specific kidney diseases and other clinical characteristics (eg, proteinuria, hypertension) on adverse pregnancy outcomes are warranted.

Key words: chronic kidney disease, fetal outcome, perinatal outcome, preeclampsia, pregnancy, pregnancy outcome

Introduction

Chronic kidney disease (CKD) is a major global public health problem associated with excessive morbidity, a decreased quality of life, and premature mortality.[1] The definitions and classifications of CKD have changed over time, with the current international guidelines defining CKD as having markers of kidney damage (eg, albumin excretion rate >30 mg/d) and/or a reduced glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 for at least 3 months duration, irrespective of the underlying cause.[2,3] The disease is then subclassified into 5 stages according

From the School of Public Health, College of Medicine and Health, University College Cork, Cork, Ireland (Mses Al Khalaf and Bodunde, Drs Maher, O'Reilly, and Khashan); The Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland (Ms Al Khalaf, Drs Maher, McCarthy, and Khashan); Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA (Dr O'Reilly); Department of Obstetrics and Gynaecology, Cork University Hospital, Cork, Ireland (Dr McCarthy); Department of Renal Medicine, Cork University Hospital, Cork, Ireland (Dr O'Shaughnessy); and School of Public Health Alumna, Cork, Ireland (Dr O'Neill).

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

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AJOG at a Glance

Why was this study conducted?

Chronic kidney disease has been linked with adverse pregnancy outcomes, but little is known about the association of adverse pregnancy outcomes with the disease severity or the underlying cause of kidney disease.

Key findings

Pregnant women with any cause of chronic kidney disease had a higher risk of preeclampsia, preterm birth, and small for gestational age babies.

Pregnant women with later stages of chronic kidney disease had worse outcomes than those with earlier stages.

What does this add to what is known?

This study estimated the overall risk of adverse pregnancy outcomes in women with chronic kidney disease and the risk of adverse outcomes according to the underlying cause, and quantified the associations between later stages of the disease (vs earlier stages) and adverse pregnancy outcomes.

The gaps in the literature such as adjusting for important factors (proteinuria, hypertension, and immunosuppressive therapies) were identified to guide future studies assessing the effect of kidney diseases on pregnancy outcomes.

to the level of kidney function as follows: stages 1 and 2 (mild CKD with an estimated GFR [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 to 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 in men.[1,4] In women aged 20−39 years, the prevalence of stages 1 and 2 and 3 to 5 of CKD are estimated to be 3% and 0.67%, respectively.[5,6]

Previous reports, many of them small in size and emanating from single centers, 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 preeclampsia, cesarean delivery (CD), preterm birth (PTB), and small for gestational age (SGA) or low birthweight (LBW) babies in women with CKD than in women without CKD.[8] However, 8 of the 14 studies examined adverse pregnancy outcomes among women with diabetes (diabetic nephropathy as an exposed group), which makes it difficult to generalize the results to women with other underlying causes of CKD. In addition, crude estimates were reported in this review without the consideration for potential confounding factors.

Previous studies evaluating the pregnancy outcomes in women with advanced stages of CKD have reported worse outcomes than in those with earlier stages, although the results were inconsistent, and the magnitude of the risk estimates differ across individual studies.[9−11] These estimates are derived from small and single-center cohorts, and we could not identify any systematic review of published data comparing the risks for adverse pregnancy outcomes in women with advanced vs earlier stages of CKD. Moreover, associations between the cause of CKD and the 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 synthesize 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.

Materials and Methods

Protocol registration and reporting

The protocol for this systematic review was prospectively registered on the International Prospective Register of Systematic Reviews (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 have a higher risk of adverse pregnancy outcomes than pregnant women without CKD?
2. Do pregnant women with late stages of CKD have a higher risk of adverse pregnancy outcomes than those at early stages?
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 or exposure group:

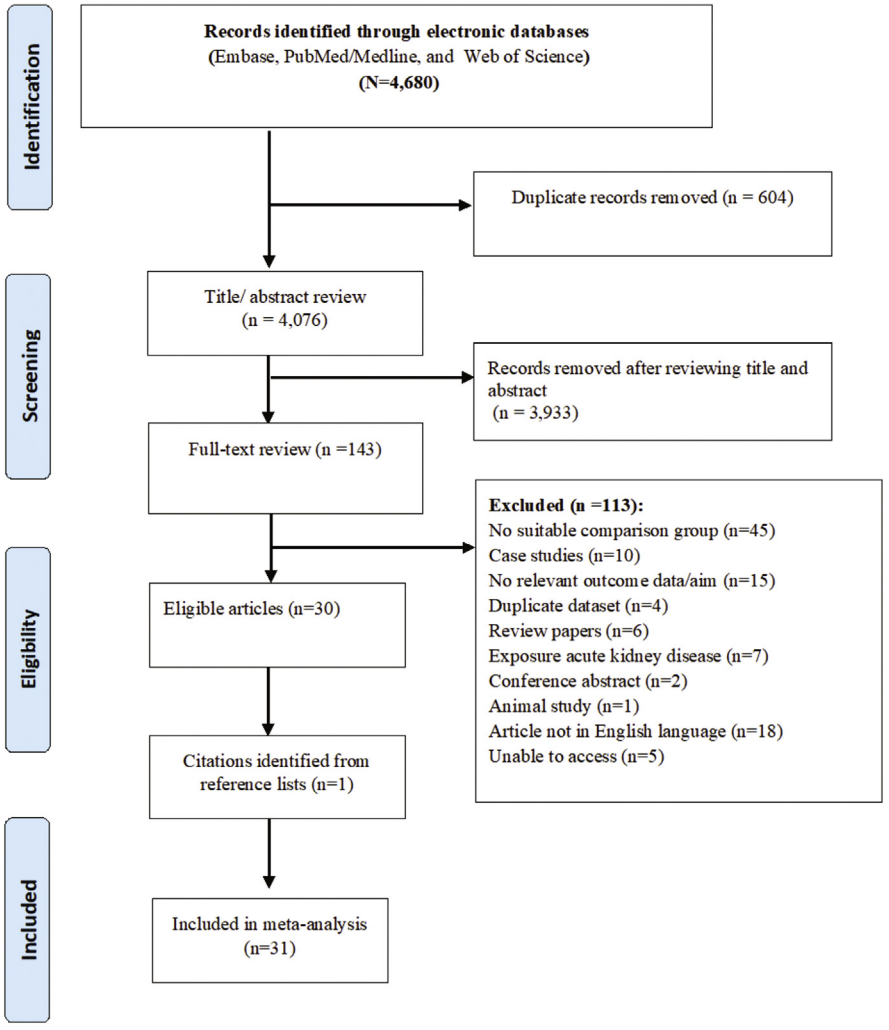
1. Pregnant women with CKD
2. Pregnant women with late stages of CKD

Comparison group:

1. Pregnant women without CKD
2. Pregnant women with early stages of CKD

Outcomes: Primary (preeclampsia, CD, 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).

FIGURE 1
PRISMA flow diagram



Flow diagram of studies on the impact of chronic kidney disease on adverse pregnancy outcome.

PRISMA, preferred reporting items for systematic reviews and meta-analyses.

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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 time of 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 presubmission updated search on May 24, 2021. The supplemental material (page 1) provides the full search strategy that was used in each database. In addition, we searched the bibliographies of the previous systematic reviews of the same topic and searched the reference lists of all the identified studies for further potentially relevant studies.

Study selection

Two reviewers (S.A.K. and E.B.) independently screened titles and abstracts, excluding the studies that clearly did not meet the predefined inclusion criteria. Full texts of potentially eligible studies were obtained and screened independently by the same 2 reviewers, and a third reviewer was consulted where consensus could not be reached. We only included the largest study where a duplicate publication of the same data (study population) existed. The process of the study selection is outlined in Figure 1.

Data extraction and quality assessment

Three reviewers performed the data extraction (E.B., G.M.M., and S.A.K.) independently using a standardized 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 the odds ratios [(ORs) and 95% confidence intervals (CI)]), and factors adjusted for, if any.

Quality assessment of the included studies was performed independently by the 3 reviewers (S.A.K., G.M.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 3 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—9).[15] We considered 0 to 3 stars as low quality, 4 to 6 stars as moderate quality, and 7 to 9 stars as high quality. Any discrepancies on screening, extraction, and quality assessment were resolved through discussion and consensus involving the 3 reviewers (S.A.K., E.B., and G.M.M.) and the lead investigator (A.S.K.).

Grading of recommendations, assessment, development, and evaluation 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 2 reviewers independently (S.A.K. and G.M.M.). The certainty of the evidence was assessed using the GRADEpro software on the basis of the

following domains: the 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), randomized controlled trials are not feasible. Therefore, the certainty of the evidence for the included studies was assessed on the basis of modifications of the traditional GRADE approach.[17,18] Thus, the included observational studies started as high quality and were downgraded accordingly on the basis of the GRADE domains.

Statistical analysis

Random-effects meta-analyses were performed using the generic inverse variance method to calculate the crude and adjusted pooled ORs of the associations between CKD and the 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 $\geq$75% were considered high heterogeneity.[19] Publication bias was evaluated using the Egger test and funnel plots. Subgroup analyses were performed according to the cause of CKD (glomerulonephritis, diabetic CKD, polycystic kidney disease [PKD] or unspecified CKD), study location (Asia, Australia, Europe, North America, or South America,) and the publication year ($\leq$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 the causes of CKD, the location, or the year of publication. Studies with "zero" event in either group were excluded from analyses.

We also conducted a posthoc 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 on the basis of a threshold of <.05. All the 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 4076 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 the inclusion criteria were excluded, leaving 30 articles for inclusion from this search. Reviewing the reference lists of the included articles identified 1 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 4 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-center 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] 10 in North America,[9,10,20,23–25,31,34,35,41] 6 in Asia,[21,22,37–39,43] 2 in Australia,[33,47] and 2 in South America.[26,28] Thirty studies reported definitions for CKD: 9 defined CKD according to the National Kidney Foundation "Kidney Disease Outcomes Quality Initiative" guidelines,[9,21,22,25,26,38,39,46,47] 11 used serum creatinine or proteinuria,[11,27–35,41] 6 used eGFR,[10,37,40,42,43,45] 4 used medical coding,[20,23,24,36] and 1 study did not report the definition of CKD.[44]

All studies scored between 4 and 8 on the Newcastle-Ottawa Scale (Supplemental Tables 1 and 2). The studies were rated as either moderate quality (n=16) or high quality (n=15); almost all the 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 the supplemental file (Supplemental Tables 1 and 2). In addition, the forest plots of all the analyses are provided in the supplement (Supplemental Figures 1–24).

Results of the meta-analyses

The effect of chronic kidney disease on adverse pregnancy outcomes (chronic kidney disease compared with no chronic kidney disease).

The summary results of all the 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 obstetrical population) as the unexposed group. The remaining 7 studies had women with other underlying medical conditions (diabetic in 6 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 preeclampsia: 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 preeclampsia, which attenuated the OR to 2.58 (95% CI, 1.33–5.01) and RD was 4.1% (95% CI, 0.09–9.7). Ten studies reported effect estimates for CD: 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 CD and that showed similar results to the unadjusted estimate, aOR, 1.65 (95% CI, 1.21–2.25); 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, 5.9–13.3). Four studies reported adjusted estimates for PTB, lowering the OR to 1.73 (95% CI, 1.31–2.27) and the RD was 3.4% (95% CI, 1.5–5.8). Similarly, a higher risk of VPTB (<34 week) was observed in the

TABLE 1
Summary results of the meta-analyses of pregnancy outcomes in women with chronic kidney disease

Maternal or fetal outcome	Crude estimates					Adjusted estimates				
	Number of studies	Number of participants	Pooled OR (95% CI)	RD (95% CI)	I^2, %	Number of studies	Number of participants	Pooled OR (95% CI)[a]	RD (95% CI)	I^2, %
Women with CKD compared with women without CKD										
Preeclampsia	15	2,782,133	8.13 (4.41–15)	16% (8.4–27)[b]	93	4	2,777,209	2.58 (1.33–5.01)	4.1% (0.9–9.7)	93
Cesarean delivery	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)[b]	92	4	2,831,929	1.73 (1.31–2.27)	3.4% (1.5–5.8)	92
VPTB (<34 wk)	10	2,833,576	4.85 (3.01–7.80)	3.1% (1.6–5.4)[b]	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)	—[b]	—	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[c]	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 with early stages of CKD										
Preeclampsia	10	833	2.77 (1.73–4.44)	24% (12–35)	31	1	126	4.50 (1.29–15.7)	35% (4.9–59)	—
Cesarean delivery	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)	0	1	126	2.03 (0.89–4.63)	17% (−2.5–37)	—
VPTB (<34 wk)	8	716	3.11 (2.06–4.69)	19% (11–29)	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)	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	—	—	—	—	—

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(continued)

TABLE 1
Summary results of the meta-analyses of pregnancy outcomes in women with chronic kidney disease *(continued)*

Maternal or fetal outcome	Crude estimates				I^2, %	Adjusted estimates			
	Number of studies	Number of participants	Pooled OR (95% CI)	RD (95% CI)		Number of studies	Number of participants	Pooled OR (95% CI)[a]	RD (95% CI)	I^2, %
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)	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: 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. The 3 studies comparing early vs late stages of CKD adjusted for proteinuria and 2 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.

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women with CKD from both the crude estimates (10 studies, OR, 4.85 [95% CI, 3.01−7.80], RD, 3.1% [95% CI, 1.6−5.4]) and adjusted estimates (4 studies, aOR, 2.18 [95% CI, 1.61−2.95], RD, 1.0% [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 (3 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 the adjusted and unadjusted results were nonsignificant (Table 1). In addition, the combined outcome of pregnancy loss showed an insignificant association with CKD (4 studies, pooled aOR, 1.58 [95% CI, 0.92−2.73], RD, 0.2% [95% CI, 0.0−0.7]).

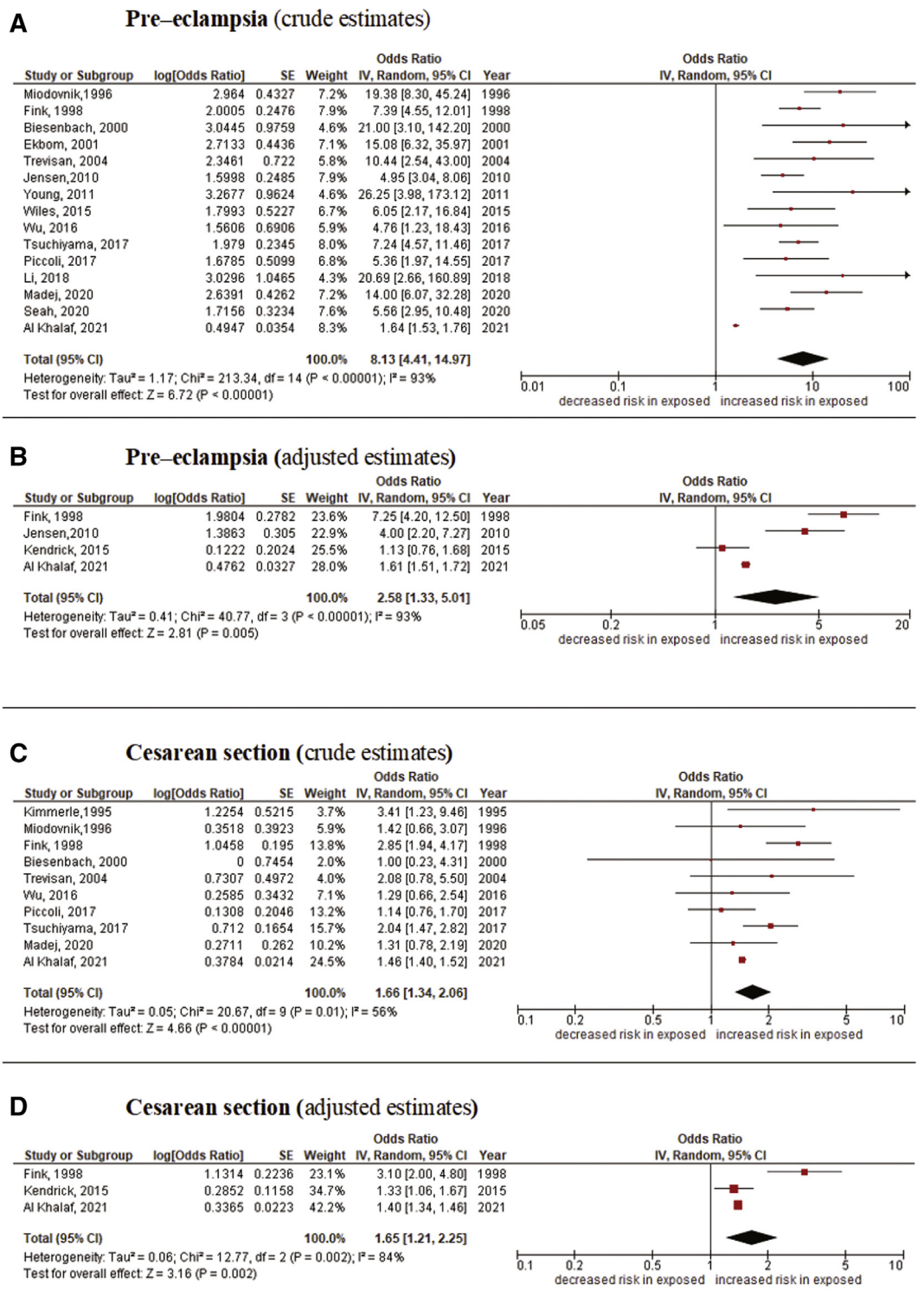
Assessment of heterogeneity and publication bias.

Heterogeneity between the studies was low for perinatal death (I^2=0%), moderate for CD (I^2=56%), and high for other outcomes. Although heterogeneity was high for most outcomes in this comparison, most effect estimates of the studies examining the effect of preeclampsia and PTB (Figures 1 and 2) are in the same direction, suggesting an association with CKD; this may indicate that heterogeneity between studies was because of poor overlapping between the studies' 95% CIs.[48] This was also explored more in the subgroup analyses on the basis of the cause of CKD, the study location, and the year of publication. For publication bias, funnel plots of preeclampsia (Supplemental Figure 1), CD (Supplemental Figure 2), PTB (Supplemental Figure 3), VPTB (Supplemental Figure 4, C), and SGA (Supplemental Figure 5) show approximately symmetrical distributions, and the results of the Egger test were nonsignificant for all outcomes (*P* values=.38;.47;.17;.10; and.44 respectively), indicating that publication bias was unlikely to be a substantial problem.

The effect of chronic kidney disease severity on adverse pregnancy outcomes (advanced stages compared with early stages of chronic kidney disease).

A summary of the results of the included studies that report adverse pregnancy

FIGURE 2
Forest plots of studies of the association between CKD and maternal complications



The *red rectangles* represent the OR for each study, and the lateral *black lines* represent the 95% CI for each study. The *diamond* represents the overall OR, and the lateral *tips of the diamond* represent the 95% CI for the combined estimates.

CI, confidence interval; *CKD*, chronic kidney disease; *OR*, odds ratio.

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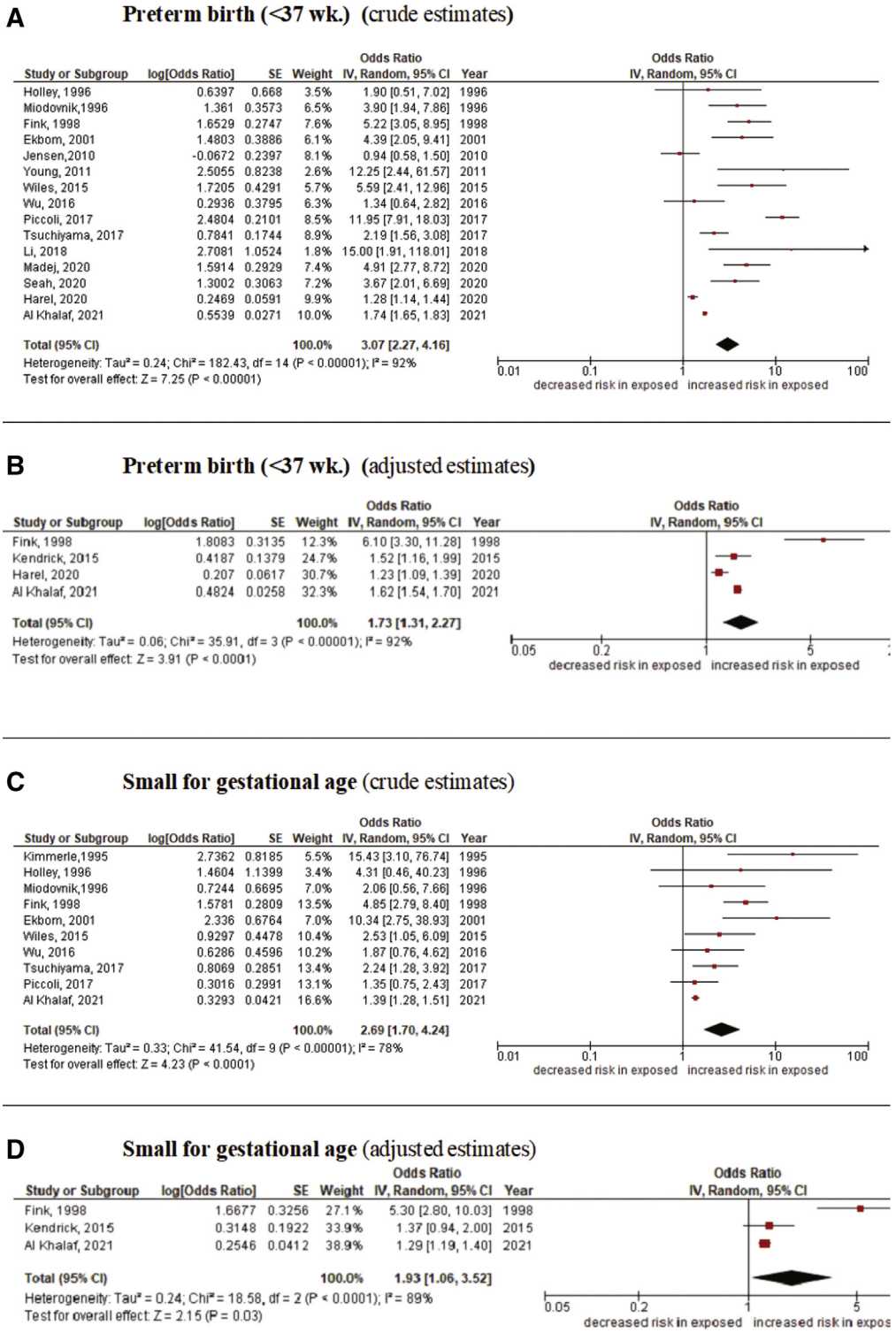
FIGURE 3
Forest plots of studies of the association between CKD and fetal or neonatal outcomes



The *red rectangles* represent the OR for each study, and the lateral *black lines* represent the 95% CI for each study. The *diamond* represents the overall OR, and the lateral *tips of the diamond* represent the 95% CI for the combined estimates.

CI, confidence interval; *CKD*, chronic kidney disease; *OR*, odds ratio.

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outcomes on the basis of the severity of kidney disease are available in Table 1. Of the 14 studies, 7 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 the creatinine level (<125 vs >125 umol/L),[11] and another study defined the severity of kidney disease according to the urine protein level[41];1 study did not report the CKD definition.[44] Only 3 studies in this comparison adjusted for potential confounders, all of them adjusted for proteinuria, and 2 of these adjusted for hypertension also.

The results suggest that the later stages of CKD, compared with the earlier stages, were associated with higher odds of preeclampsia (10 studies; crude OR, 2.77 [95% CI, 1.73−4.44], RD, 24% [95% CI, 12−35]), CD (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, 26−42]), and VPTB (8 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 (3 studies; aOR, 2.42 [95% CI, 0.82−7.15], RD, 17% [95% CI, −2.8−43]).

The risks of LBW (3 studies; crude OR, 3.17 [95% CI, 1.05−9.62], RD, 22% [95% CI, 0.7−49]) and NICU admission (3 studies; crude OR, 2.94 [95% CI, 1.65−5.24], 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 the later stages of CKD compared with 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 preeclampsia (n=1) and VPTB (n=2) (Table 1).

Assessment of heterogeneity and publication bias.

Heterogeneity among the studies was low in the studies that assessed the outcomes including stillbirth, neonatal death, perinatal death, pregnancy loss, PTB, VPTB, NICU admission, (I^2=0%) and CD (I^2=21%). A moderate level of heterogeneity was observed between the studies examining the effects of preeclampsia (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 because of a poor overlapping of the 95% CIs for the effect estimates of the individual studies. The tests for funnel asymmetry were nonsignificant for preeclampsia (*P*=.14), CD (*P*=.50), and SGA (*P*=.61), suggesting that publication bias is not a concern (Supplemental Figures 9, B; 10, B; and 13,C, respectively). However, there was little evidence for small-study effects for PTB (*P*=.032) (Supplemental Figure 11, B).

The effect of the cause of chronic kidney disease on adverse pregnancy outcomes

When we investigated the risk of adverse pregnancy outcomes on the basis of the cause of CKD, we determined that all the causes were associated with a higher risk of preeclampsia, PTB, and SGA (Table 2 & Supplemental Figures 19, 21, and 23). Adjustment for confounding factors in this analysis refers mainly to maternal demographic characteristics and other comorbidities.

The magnitude of the risk of preeclampsia 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 the 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 CD (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 preeclampsia (*P*=.03), VPTB (*P*<.00001), and SGA (*P*=.008). In addition, 1 study reported the effect estimate for women with renovascular CKD, compared with normotensive women without CKD, which suggested higher odds of preeclampsia (aOR, 3.64 [95% CI, 2.18−6.09]), indicated PTB (aOR, 8.09 [95% CI, 5.73−11.4]), and SGA (aOR, 0.328 [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 22 and 23). When this was further investigated, a high level of heterogeneity for PTB that was observed in the diabetic CKD subgroup (n=6, I^2=96%) was owing to 2 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 preeclampsia analysis decreased heterogeneity. The explanation for outlier results in these studies might be explained by the studies inclusion criteria, as 1 study included women with microalbuminuria without reduced eGFR,[27] whereas the other study compared the outcomes to the general obstetrical population and not mainly to 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 the subgroup analyses by publication year (≤2010 vs >2010), showed a significant decreased risk over time for CD (*P*=.02) and SGA (*P*<.0001) and also explained some of the heterogeneity among the studies (Supplemental

TABLE 2
Summary results of the meta-analyses of adverse pregnancy outcomes in women with chronic kidney disease compared with women without chronic kidney disease according to the cause of chronic kidney disease

	Crude estimates					Adjusted estimates				
Maternal or fetal outcome	Number of studies	Number of participants	Pooled OR (95% CI)	RD (95% CI)	I^2, %	Number of studies	Number of participants	Pooled OR (95% CI)[a]	RD (95% CI)	I^2, %
Preeclampsia										
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
Cesarean delivery										
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
VPTB <34 wk										
Glomerulonephritis CKD	2	1931	19.2 (10.4–35.5)	15% (8.4–25)	0	—	—	—	—	—
Diabetic CKD	5	1558	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										

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(continued)

TABLE 2

Summary results of the meta-analyses of adverse pregnancy outcomes in women with chronic kidney disease compared with women without chronic kidney disease according to the cause of chronic kidney disease *(continued)*

	Crude estimates					Adjusted estimates				
Maternal or fetal outcome	Number of studies	Number of participants	Pooled OR (95% CI)	RD (95% CI)	I^2, %	Number of studies	Number of participants	Pooled OR (95% CI)[a]	RD (95% CI)	I^2, %
Glomerulonephritis CKD	—	—	—	—	—	—	—	—	—	—
Diabetic CKD	1	43	4.00 (0.80–20.1)	24% (−2.2–62)	—	—	—	—	—	—
PKD	—	—	—	—	—	—	—	—	—	—
Unspecified CKD	—	—	—	—	—	1	1556	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	1556	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	1556	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

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Table 3). However, no differences were found on the basis of the study location (Supplemental Material, pages 31−32).

Grading of recommendations, assessment, development, and evaluation certainty of the evidence

Considering that our review included observational studies, the certainty of the evidence was judged to be "low" for preeclampsia, PTB, and VPTB, and "very low" for SGA and CD. Therefore, the certainty of the evidence overall across all the outcomes was judged to be very low. The evidence was downgraded (depending on the outcome of interest) because of a serious risk of bias in the included studies (the 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 (because of a moderate level of heterogeneity that was not explained by subgroup analyses and effect estimates in varying directions and crossing the line of no effect). Details about the GRADE evaluation are provided in Table 3.

Comment

Principal findings

This systematic review and meta-analysis of 31 international studies over the last 4 decades examined the associations between prepregnancy CKD and the risk of adverse pregnancy outcomes. We identified 3 main findings. First, we confirmed that CKD is a strong risk factor for adverse pregnancy outcomes. For example, the odds for preeclampsia were 8-fold higher in women with CKD than in women without CKD and remained approximately 3-fold higher after adjusting for factors including the maternal age, smoking, body mass index, parity, and other comorbidities. Second, we confirmed that the later stages of CKD are associated with a greater risk of adverse pregnancy outcomes than the 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, the risks were higher among women with diabetic CKD, particularly for CD, PTB, and SGA.

Comparison with existing literature

Our review reinforces the previous findings on the occurrence of adverse pregnancy outcomes in women with CKD compared with 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 with those with early stages. In addition, a previous review reported a high quality of the evidence for preeclampsia and PTB and low for SGA/LBW,[8] but our GRADE evaluation showed a 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 because of 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 of 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, CD, and SGA, and the magnitude of the effect estimates varies among included studies on the basis of the albuminuria level (microalbuminuria/macroalbuminuria). The pregnancy outcomes among pregnant women with PKD were reported in 2 studies, and they showed an association with preeclampsia, CD, 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 preeclampsia (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 the 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 the cause of CKD, and the inclusion of studies from multiple geographic regions spanning 4 decades. In addition, each process of the systematic review was carried out by at least 2 independent reviewers using standardized 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 gray literature was not

TABLE 3
Certainty of the evidence assessed using the grading of recommendations, assessment, development, and evaluation approach for chronic kidney disease and adverse pregnancy outcomes

		Certainty assessment					Summary of findings				
							Study event rates (%)		Relative effect (95% CI)[a]	Anticipated absolute effects	
Outcome	Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Overall certainty of evidence	No CKD	CKD		Risk with no CKD	Risk difference with CKD
Preeclampsia[b]	16	Serious[c]	Not serious	Not serious	Serious[d]	⊕⊕⊕◯◯ Low	76,290/ 2,759,512 (2.8%)	1299/24,033 (5.4%)	OR, 6.79 (3.93–11.8)	28 per 1000	134 more per 1000 (from 73 more to 222 more)
Preterm birth (<37 wk)[b]	16	Serious[c]	Not serious[e]	Not serious	Serious[d]	⊕⊕◯◯ Low	145,725/ 2,812,368 (5.2%)	2612/26,949 (9.7%)	OR, 2.88 (2.16–3.83)	52 per 1000	84 more per 1000 (from 54 more to 121 more)
Small for gestational age	11	Serious[c]	Serious[f]	Not serious	Serious[d]	⊕◯◯◯ Very low	70,589/ 2,758,432 (2.6%)	929/23,966 (3.9%)	OR, 2.36 (1.61–3.47)	26 per 1000	33 more per 1000 (from 15 more to 58 more)
Cesarean delivery	11	Serious[c]	Serious[g]	Not serious	Serious[d]	⊕◯◯◯ Very low	327,224/ 2,758,410 (11.9%)	4460/23,961 (18.6%)	OR, 1.58 (1.32–1.88)	119 per 1000	57 more per 1000 (from 32 more to 83 more)
VPTB (<34 wk)[b]	11	Serious[c]	Not serious	Not serious	Serious[d]	⊕⊕◯◯ Low	23,648/ 2,808,571 (0.8%)	708/26,417 (2.7%)	OR, 4.70 (2.92–7.57)	8 per 1000	30 more per 1000 (from 16 more to 52 more)

CI, confidence interval; *CKD*, chronic kidney disease; *OR*, odds ratio; *VPTB*, very preterm birth.

[a] The pooled odds ratios presented are a combination of adjusted (when reported by included studies) and crude effect estimates; [b] One study (Seah et al,[33] 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 for this information proved unsuccessful; [c] Downgraded 1 level for the risk of bias (the included studies were observational, a few studies reported the adjusted effect estimates and confounding was judged to be a serious concern); [d] Downgraded 1 level for imprecision (the included studies had very wide 95% confidence intervals); [e] Although the heterogeneity levels between the studies were high (I^2=92), almost all the estimates from the forest plots consistently supported associations in the same direction; [f] Downgraded 1 level for inconsistency (because of a moderate level of heterogeneity that was not explained by subgroup analysis and effect estimates in varying these directions and crossing the line of no effect); [g] Downgraded 1 level for inconsistency (because of varying directions of effect estimates and some estimates crossing the line of no effect. Although the heterogeneity was high, it was mainly because of different causes of CKD).

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searched. Although we evaluated the crude and adjusted estimates that highlighted significant confounding when comparing the estimates, most of the included studies reported crude estimates only, and they were performed in a single center and were of a small sample size. Nevertheless, by pooling the results of these individual studies, we aimed to better estimate the true magnitude of the risk. The confounding factors were addressed in 9 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 the outcomes was judged to be "very low" using the GRADE approach (certainty was downgraded because of 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 the under- or overdiagnosis of preeclampsia 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. In addition, the data on preeclampsia were not detailed enough to investigate whether the magnitude of risk associated with CKD varied by the preeclampsia severity (severe vs mild, or term vs preterm). Similarly, the data on CD were reported as overall deliveries in most studies without distinguishing between elective or emergency CD.

Women with CKD are considered as a high-risk group during pregnancy and should be offered preconception counseling 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 the RDs depending on the severity and the cause of CKD, this systematic review will enable clinicians to better tailor care and counseling to individual patient risk. Future studies examining the 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 the factors (proteinuria, hypertension, immunosuppressive therapies, disease activity) that might mediate this risk.

Conclusions

The results of this meta-analysis confirmed an association between prepregnancy CKD and adverse pregnancy outcomes, with different risks according to the cause and the severity of CKD. We hope that these findings will support the clinicians aiming to counsel women having CKD and 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 characterize women with CKD in early pregnancy and prospectively collect data on a core set of standardized pregnancy outcomes. Such an initiative would accurately quantify the absolute risks and the identify risk factors for adverse pregnancy outcomes in women with CKD, enabling pregnancy counseling to be better tailored to individual patient risk and generating hypotheses to be tested in future interventional studies. ■

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Supplemental Material

Supplemental methods

Search strategy for Web of Science.

1. Pregnancy outcome* OR obstetric outcome* OR birth outcome* OR pregnancy complication* OR gestational complication*or obstetric complication OR birth complication* OR labor complication* OR pre-term deliver* OR preterm deliver* OR pre-term birth*or preterm birth* OR preterm labor* OR pre-term labor* OR premature deliver* OR premature birth* OR premature labor* OR prematurity OR cesarean* OR cesarean section* OR csection* OR c section* OR spontaneous abortion* abortion OR pregnancy loss OR miscarriage* OR miscarry OR stillbirth* OR still birth* OR intrauterine death* OR intra-uterine death* OR fetal death* OR fetal mortalit* OR neonatal mortalit* OR neonatal death* OR newborn death* OR newborn mortalit* OR new born death* OR new born mortalit* OR perinatal mortalit* OR perinatal death* OR infant mortalit* OR infant death* pre-eclampsia OR preeclampsia OR pre eclampsia OR preeclamptic OR pre eclamptic OR pre-eclamptic toxemia* OR preeclamptic toxemia* OR PET OR pregnancy toxemia* OR toxemia* OR eclampsia/ OR eclamptic OR HELLP OR hemolysis elevated liver enzymes low platelet count OR hemolysis-elevated liver enzymes-low platelet count OR fetal outcome* OR fetal complication* OR neonate complication* OR neonatal complication*or newborn complication* gestational age* OR special care baby unit admission* OR SCBU admission* OR NICU admission* OR neonatal intensive care unit admission* OR small for gestational age* OR SGA* OR IUGR* OR intrauterine growth restriction* OR LBW*or low birth weight* OR VLBW* OR very low birth weight*
2. Chronic Kidney Insufficien* OR CKD OR Chronic Kidney disease OR Chronic renal disease OR Chronic renal Insufficien* OR dialysis OR kidney failure OR renal failure OR diabetic kidney disease OR diabetic chronic kidney disease OR diabetic nephropathy* OR diabetic renal disease OR congenital renal disease OR congenital kidney disease OR polycystic kidney disease OR PKD OR CAKUT OR congenital anomalies of kidney and urinary tract OR Tubulointerstitial CKD OR Glomerular CKD OR proteinuric CKD Hypertensive CKD OR hypertensive kidney disease OR renovascular disease
3. Searches 1 and 2 were then combined (1 'AND' 2)

Search strategy for Embase.

1. 'pregnancy outcome' OR 'pregnancy complications' OR 'high risk pregnancy' OR 'labor' OR 'delivery' OR 'fetus outcome' OR 'parameters concerning fetus newborn pregnancy' OR 'premature labor' OR 'immature and premature labor' OR 'prematurity' OR 'cesarean section' OR 'spontaneous abortion' OR 'stillbirth' OR 'fetus death' OR 'infant mortality' OR 'fetus mortality' OR 'maternal mortality' OR 'perinatal mortality' OR 'preeclampsia' OR 'eclampsia' OR 'eclampsia and preeclampsia' OR 'hellp' OR 'disseminated intravascular coagulation' OR 'newborn death' OR 'gestational age' OR 'infant low birth weight" OR 'low birth weight' OR 'very low birth weight' OR 'extremely low birth weight' OR 'newborn intensive care' OR 'small for date infant' OR 'pregnancy outcome*' OR 'maternal outcome*' OR 'pregnancy complication*' OR 'high risk pregnanc*' OR 'obstetric outcome*' OR 'obstetric complication*' OR 'normal birth*' OR 'live birth*' OR 'premature birth*' OR 'preterm birth*' OR 'preterm deliver*' OR 'born preterm' OR 'cesarean*' OR 'csection*' OR 'miscarriage*' OR 'stillbirth*' OR 'intrauterine death*' OR 'special care baby unit admission*' OR 'scbu admission*' OR 'neonatal intensive care unit admission*' OR 'nicu admission*' OR 'sga' OR 'iugr' OR 'neonatal intraventricular haemorrhage' OR 'neonatal intraventricular hemorrhage' OR 'apgar score' OR 'lbw' OR 'vlbw'
2. 'chronic Kidney Insufficien*' OR 'CKD' OR 'Chronic Kidney disease' OR 'Chronic renal disease' OR 'Chronic renal Insufficien*' OR 'dialysis or kidney failure' OR 'renal failure' OR 'diabetic kidney disease' OR 'diabetic chronic kidney disease' OR 'diabetic nephropathy' or 'diabetic renal disease' OR 'congenital renal disease' OR 'congenital kidney disease' OR 'polycystic kidney disease' OR 'PKD' OR 'CAKUT' OR 'congenital anomalies of kidney and urinary tract' OR 'Tubulointerstitial CKD' OR 'Glomerular CKD' OR 'proteinuric CKD' OR 'Hypertensive CKD' OR 'hypertensive kidney disease' OR 'renovascular disease')
3. Pregnan*
4. Searches 1, 2 and 3 were then combined (1 'AND' 2 'AND' 3)

Search strategy for PubMed using MeSH term.

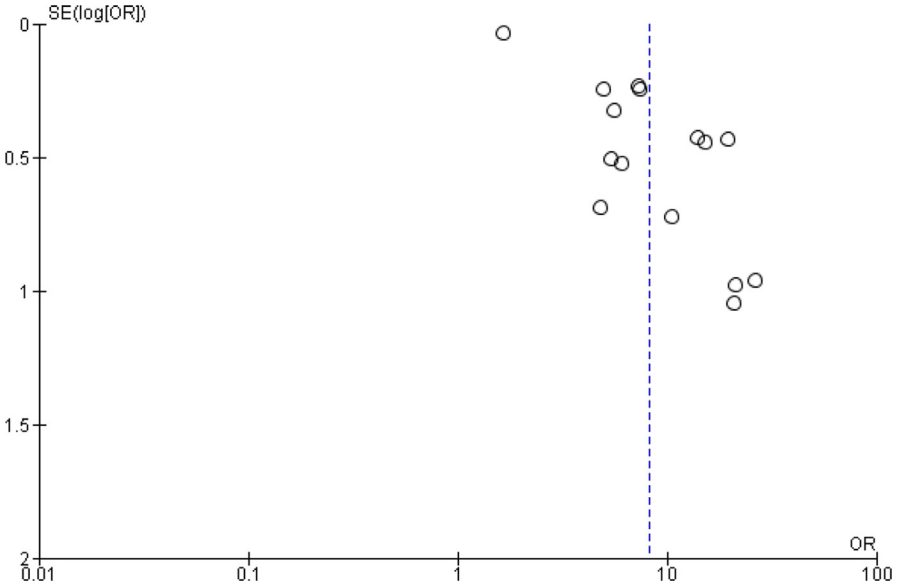
1. "Pregnancy" OR "pregnancy, high risk" OR "pregnancy complications, OR "infant, low birth weight" OR "infant, extremely low birth weight" OR "infant, very low birth weight" OR "infant, small for gestational age" OR "obstetric labor, premature" OR "infant, premature" OR "infant, extremely premature" OR "Stillbirth" OR "Stillbirth" OR "abortion, spontaneous" OR "Pre-Eclampsia" OR "Eclampsia" OR "HELLP Syndrome" OR "Cesarean Section" OR "Fetal Death" OR "Pregnancy Outcome" OR "Pregnancy Complications" OR "Perinatal Mortality" OR "Infant Death" OR "Infant Mortality" OR "intensive care units, neonatal" OR "infant, newborn" OR "Intensive Care Units" OR "Fetal Growth Retardation" OR "abortion, induced"
2. "Diabetic Nephropathies" OR "Fused Kidney" OR "Cakut" OR "Polycystic Kidney" OR "Renal Insufficiency, Chronic" OR "Hypertension, Renovascular" OR "Nephropathy, Chronic Tubulointerstitial"
3. Searches 1 and 2 were then combined (1 'AND' 2)

Supplemental figures

Forest plots and funnel plots of the association between chronic kidney disease and adverse pregnancy outcomes (chronic kidney disease vs no chronic kidney disease comparison).

SUPPLEMENTAL FIGURE 1

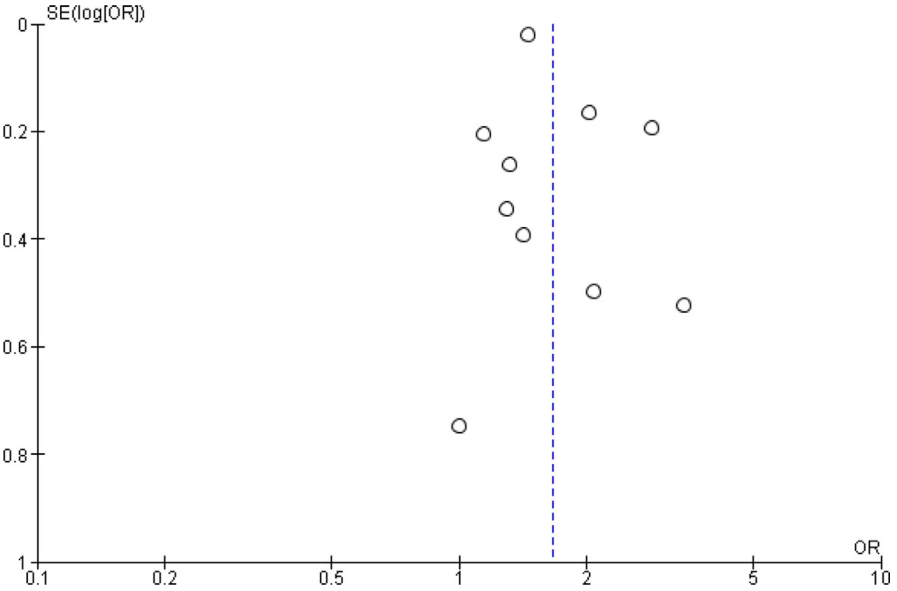
Funnel plot of preeclampsia (crude estimates)



OR, odds ratio; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

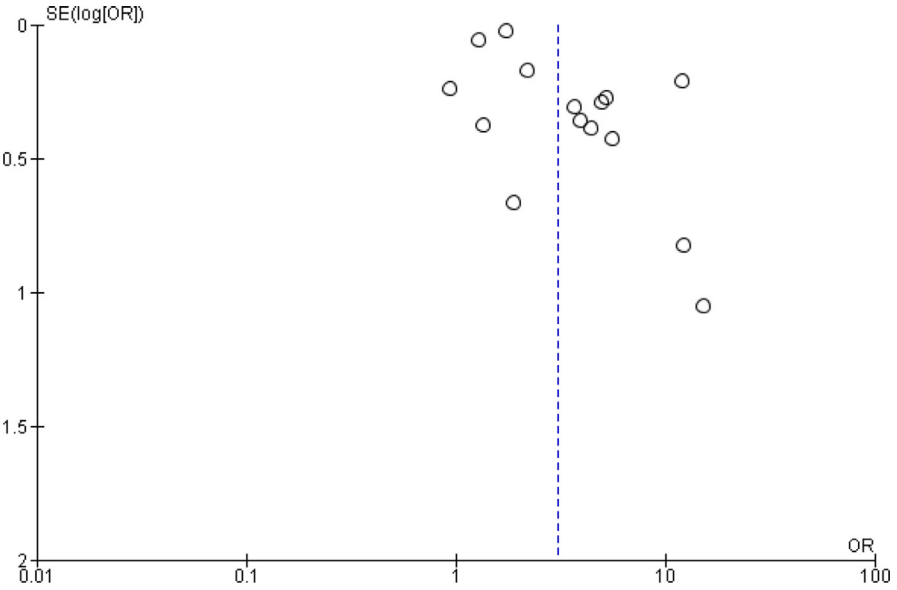
SUPPLEMENTAL FIGURE 2
Funnel plots of cesarean delivery (crude estimates)



OR, odds ratio; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

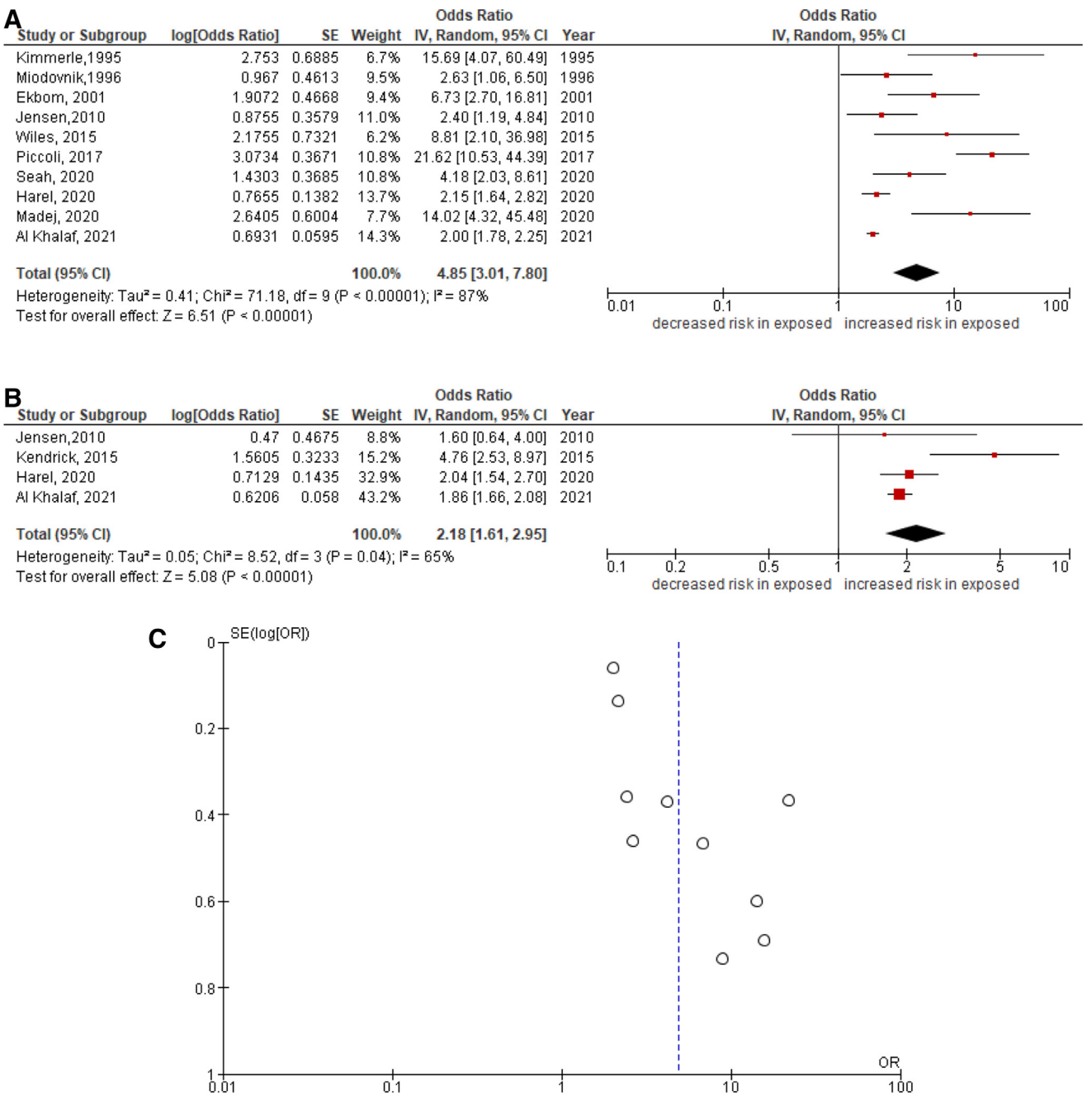
SUPPLEMENTAL FIGURE 3
Funnel plot of preterm birth (crude estimates)



OR, odds ratio; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 4
Forest plots and funnel plot

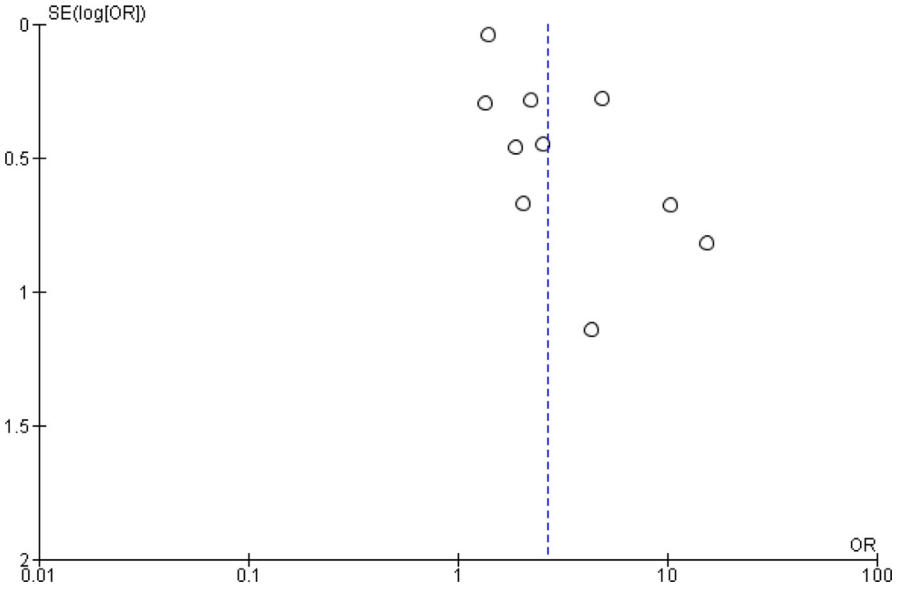


A, Forest plot of crude estimates for VPTB (<34 weeks' gestation); **B,** Forest plot of adjusted estimates for VPTB (<34 weeks' gestation); **C,** Funnel plot of VPTB (crude estimates).

CI, confidence interval; *IV*, inverse variance; *SE*, standard error; *VPTB*, very preterm birth.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

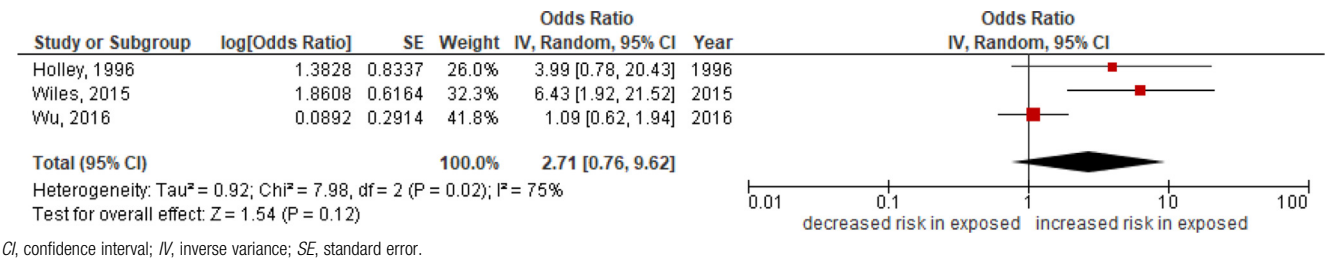
SUPPLEMENTAL FIGURE 5
Funnel plots of small for gestational age (crude estimates)



OR, odds ratio; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

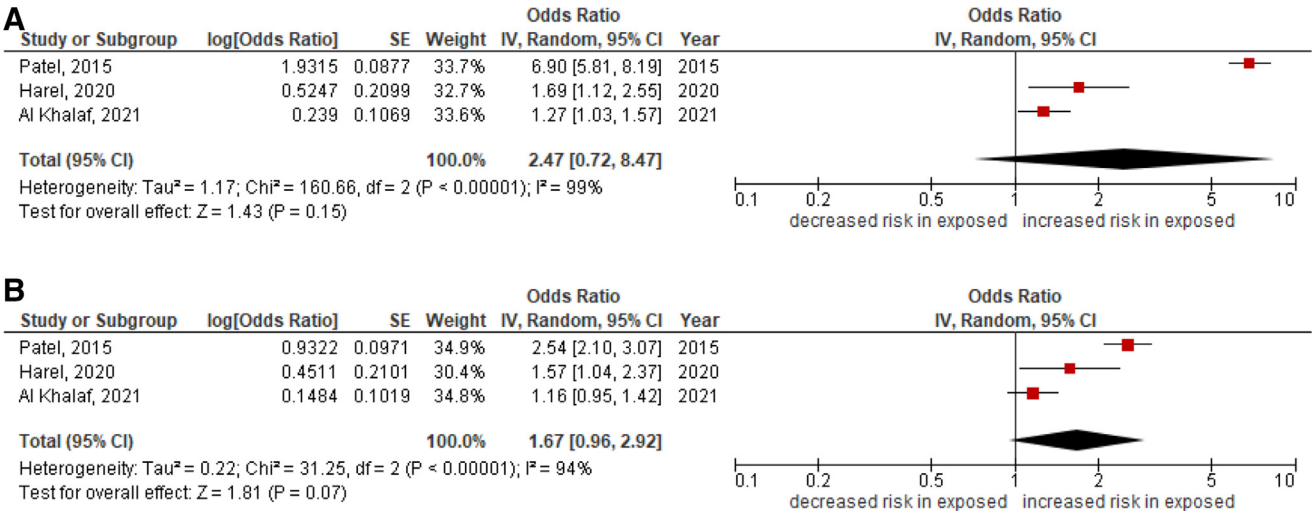
SUPPLEMENTAL FIGURE 6
Forest plot of crude estimates for miscarriage



CI, confidence interval; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 7
Forest plots

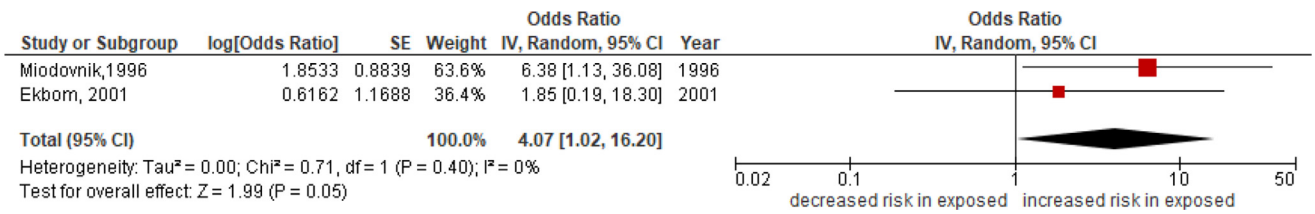


Forest plots of (**A**) crude estimates for stillbirth death and (**B**) adjusted estimates for stillbirth death.

CI, confidence interval; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 8
Forest plot of crude estimates for perinatal death

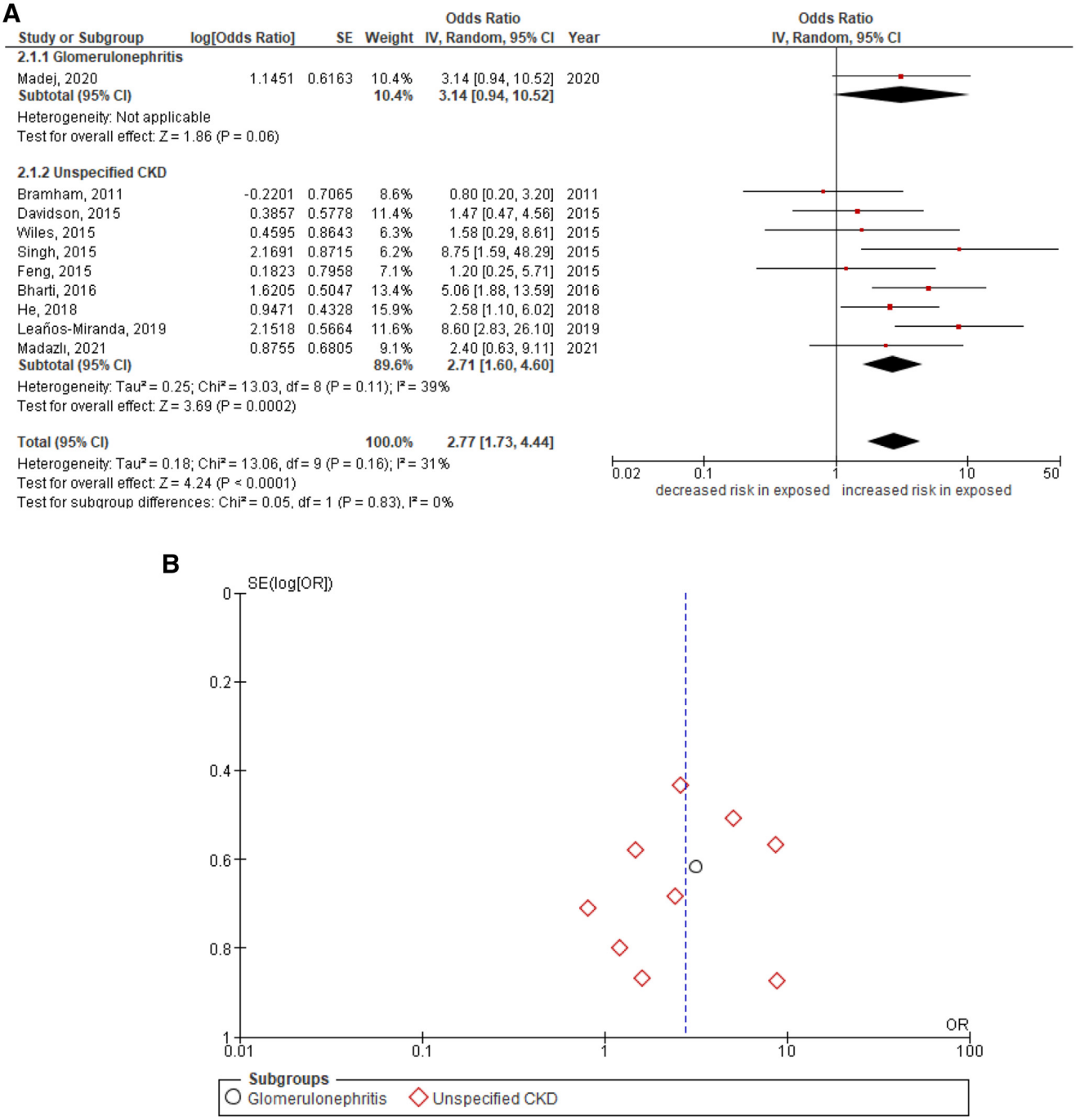


CI, confidence interval; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

Forest plots of the association between chronic kidney disease and adverse pregnancy outcomes (late vs early stages of chronic kidney disease).

SUPPLEMENTAL FIGURE 9
Forest plots

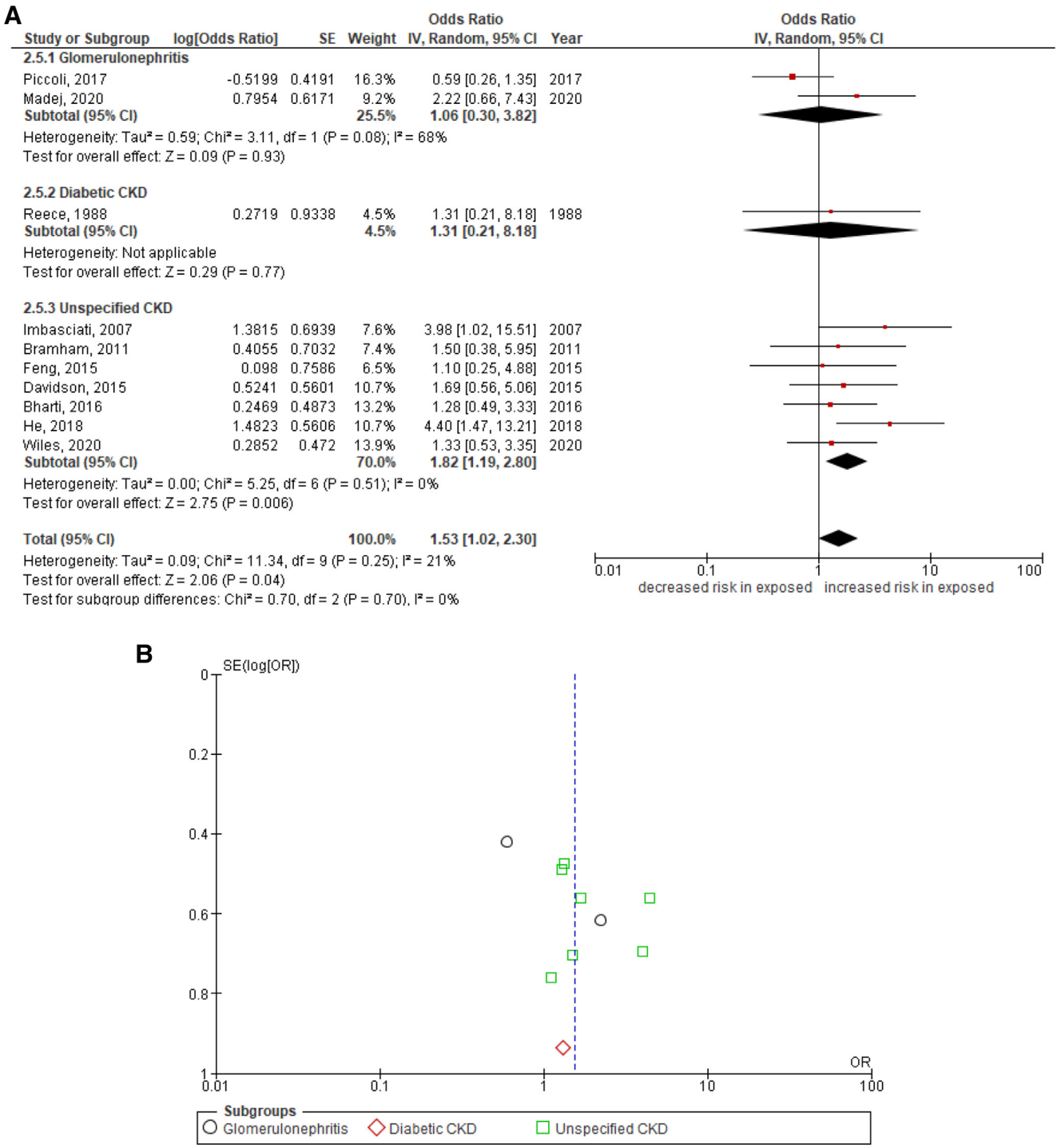


Forest plots of (**A**) crude estimates for preeclampsia and (**B**) preeclampsia (crude estimates).

CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *OR*, odds ratio; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 10
Forest plots

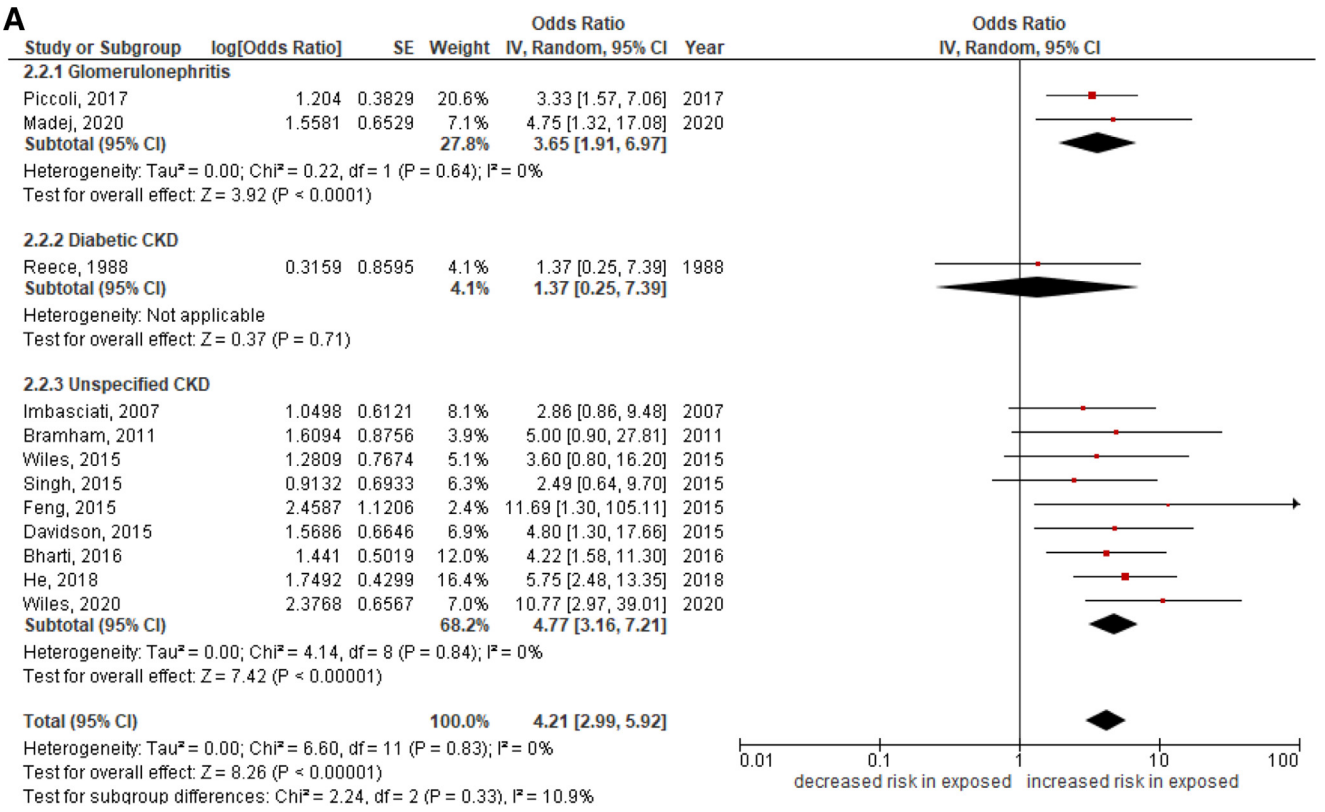


Forest plots of (**A**) crude estimates CD and (**B**) CD (crude estimates).

CI, confidence interval; *CD*, cesarean delivery; *CKD*, chronic kidney disease; *IV*, inverse variance; *OR*, odds ratio; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 11
Forest plots

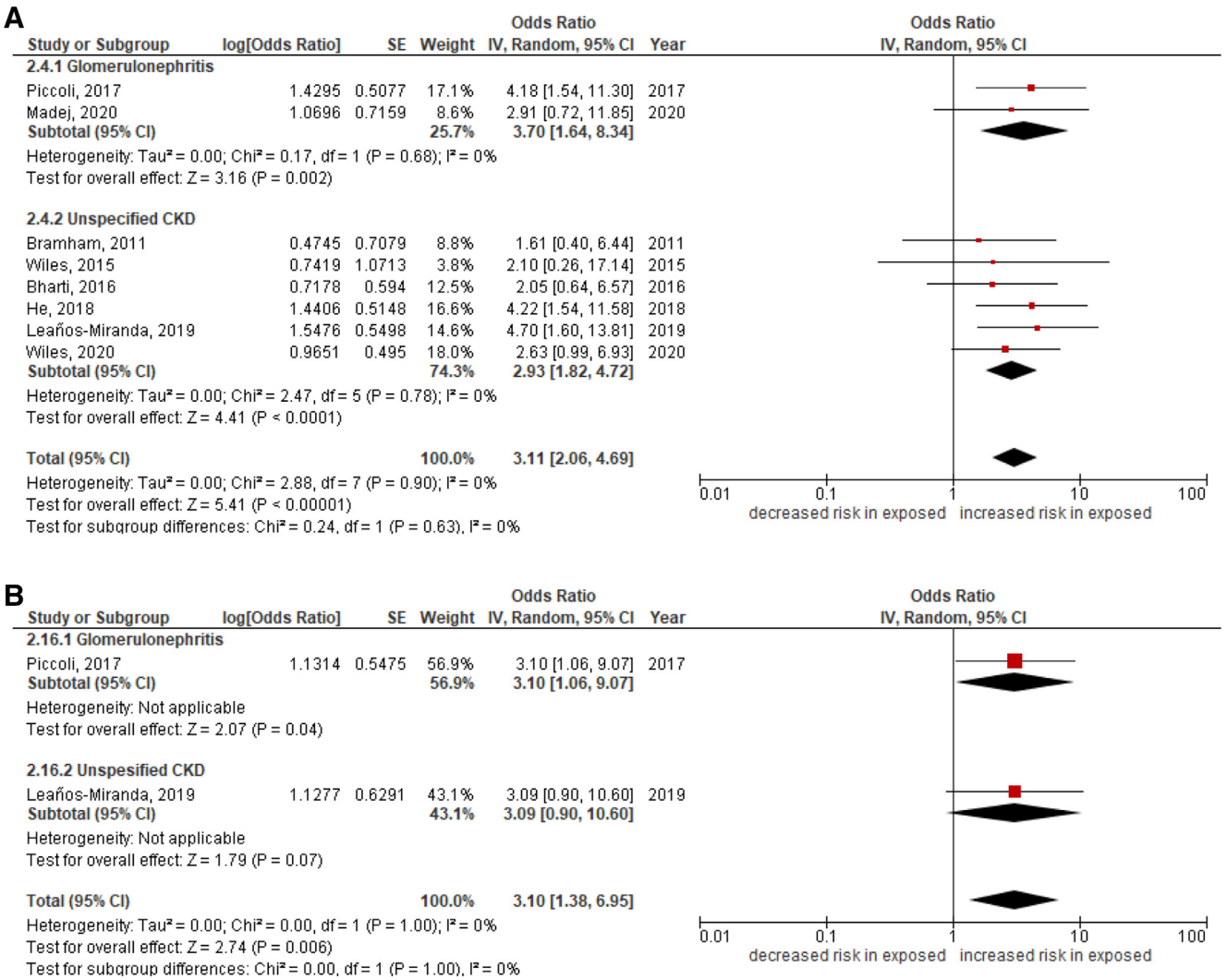


Forest plots of (**A**) crude estimates for preterm birth (<37 weeks' gestation) and (**B**) preterm birth (<37 weeks' gestation).

CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *OR*, odds ratio; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 12
Forest plots

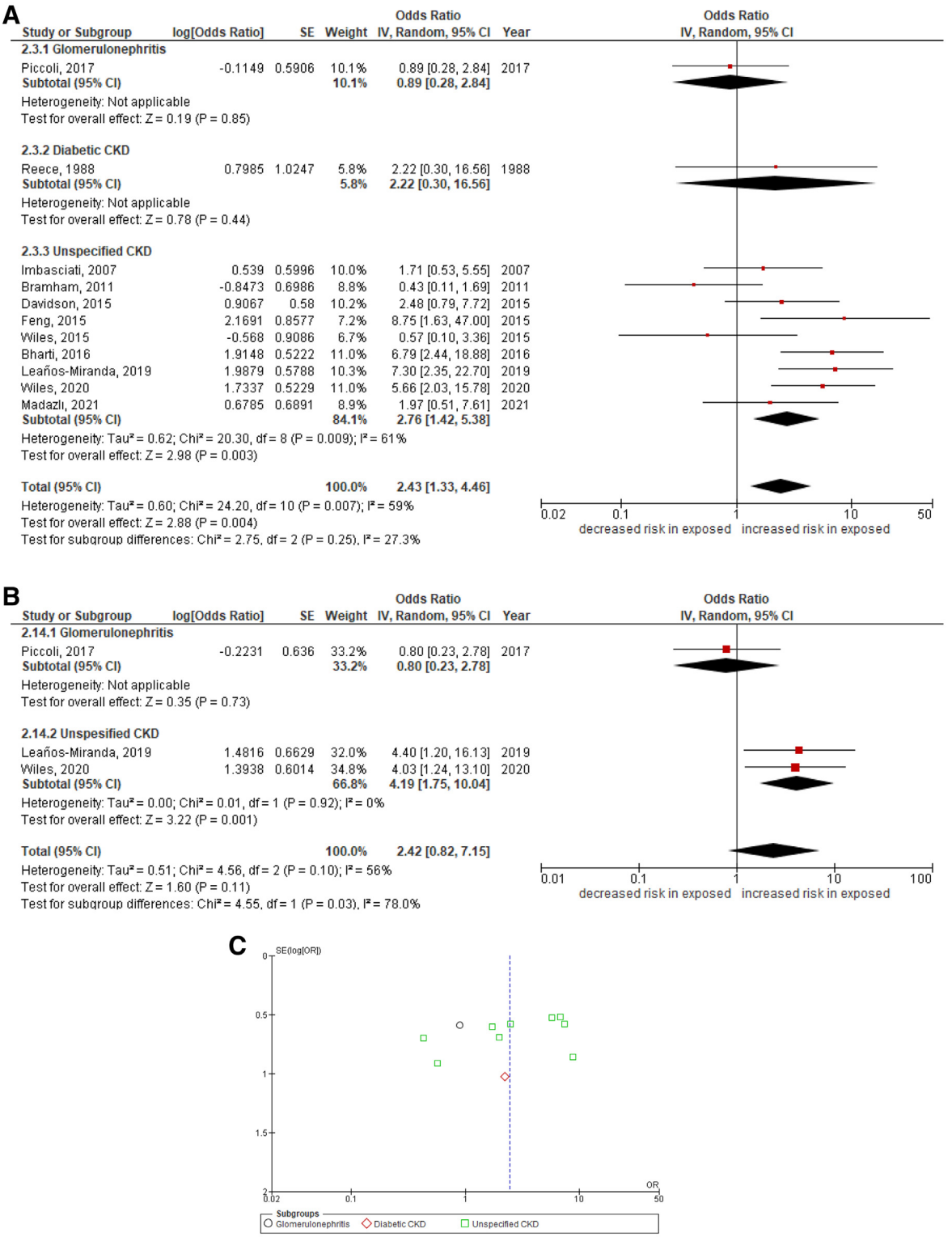


Forest plots of (**A**) crude estimates for VPTB (<34 weeks' gestation) and (**B**) adjusted estimates for VPTB (<34 weeks' gestation).

CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error; *VPTB*, very preterm birth.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 13
Forest plots

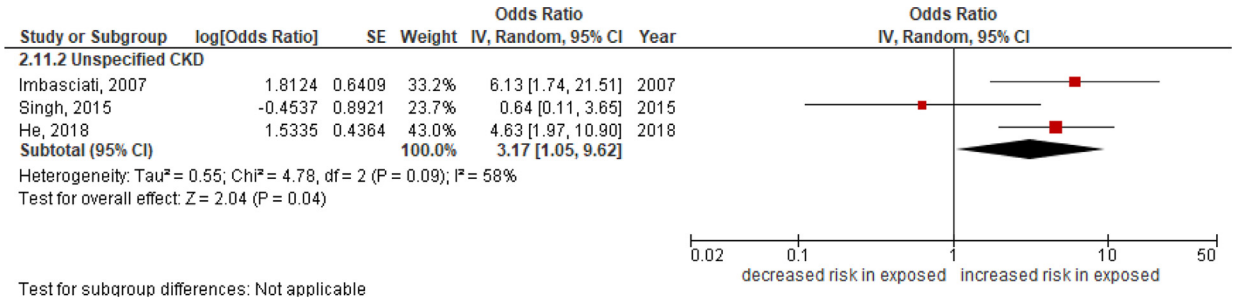


Forest plots of (**A**) crude estimates for SGA; (**B**) adjusted estimates for SGA and (**C**) SGA.

CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *OR*, odds ratio; *SE*, standard error; *SGA*, small for gestational age.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

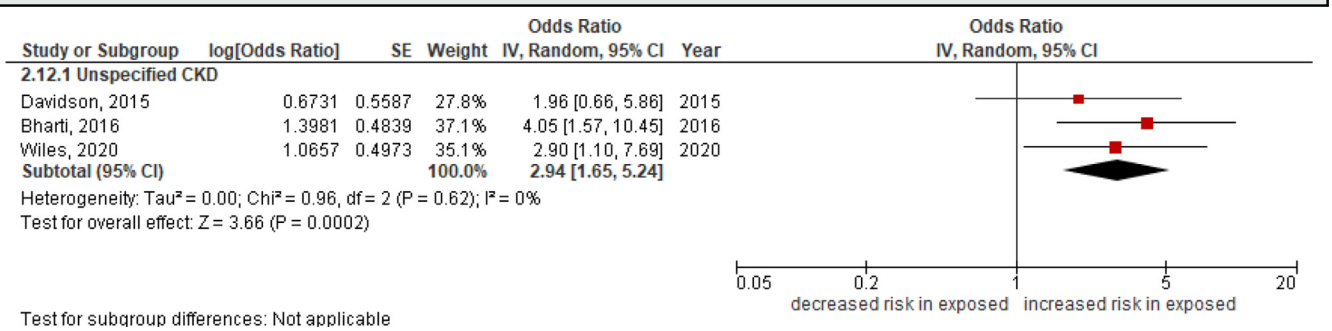
SUPPLEMENTAL FIGURE 14
Forest plot of crude estimates for low birthweight



CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

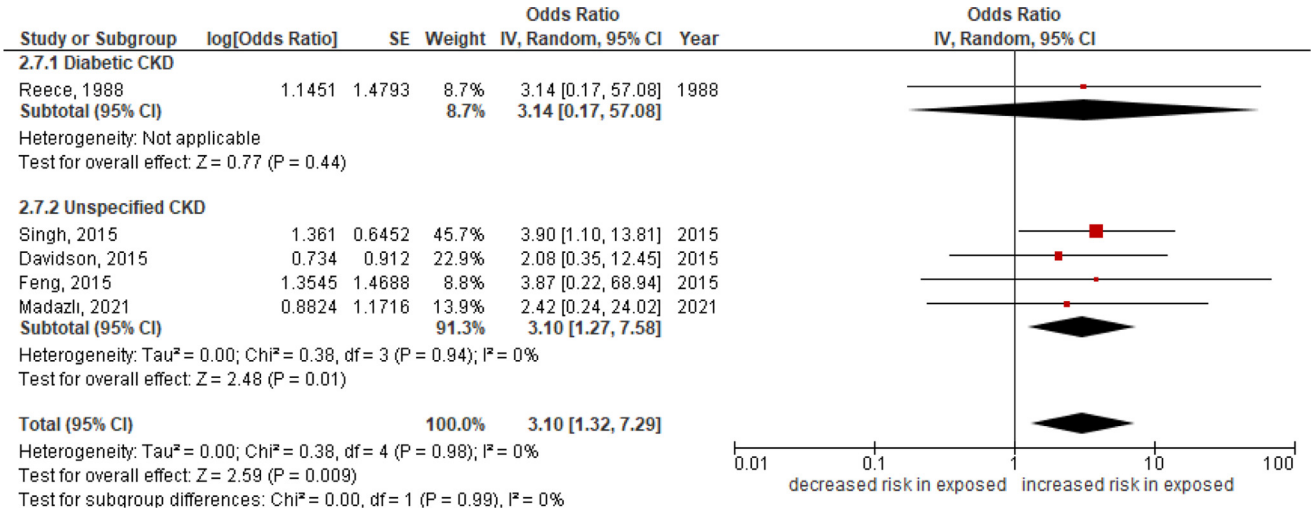
SUPPLEMENTAL FIGURE 15
Forest plot of crude estimates for neonatal intensive care unit admission



CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

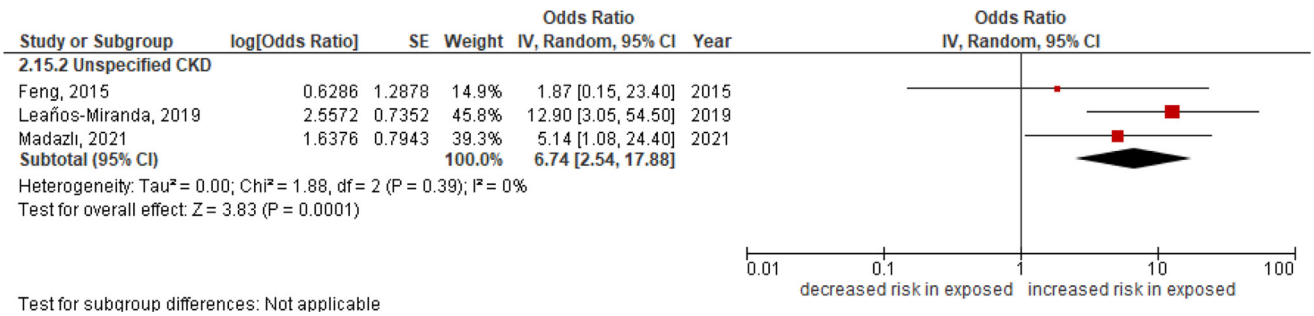
SUPPLEMENTAL FIGURE 16
Forest plot of crude estimates for stillbirth



CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

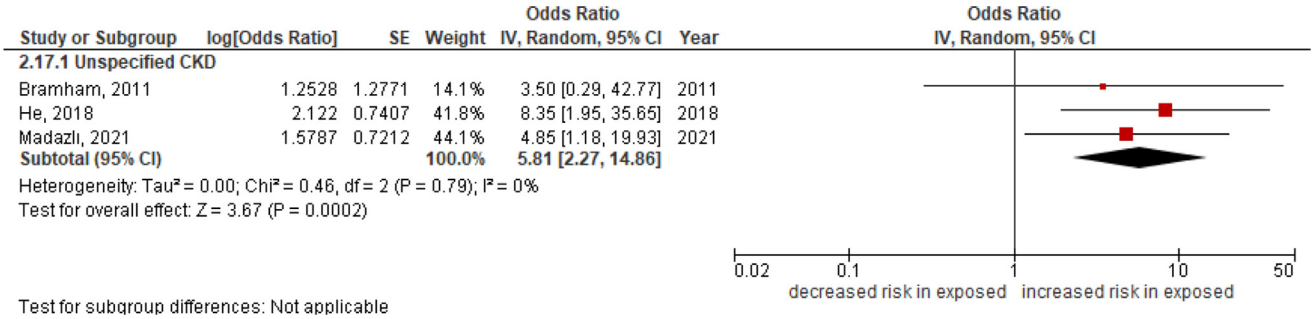
SUPPLEMENTAL FIGURE 17
Forest plot of crude estimates for neonatal death



CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 18
Forest plot of crude estimates for perinatal death

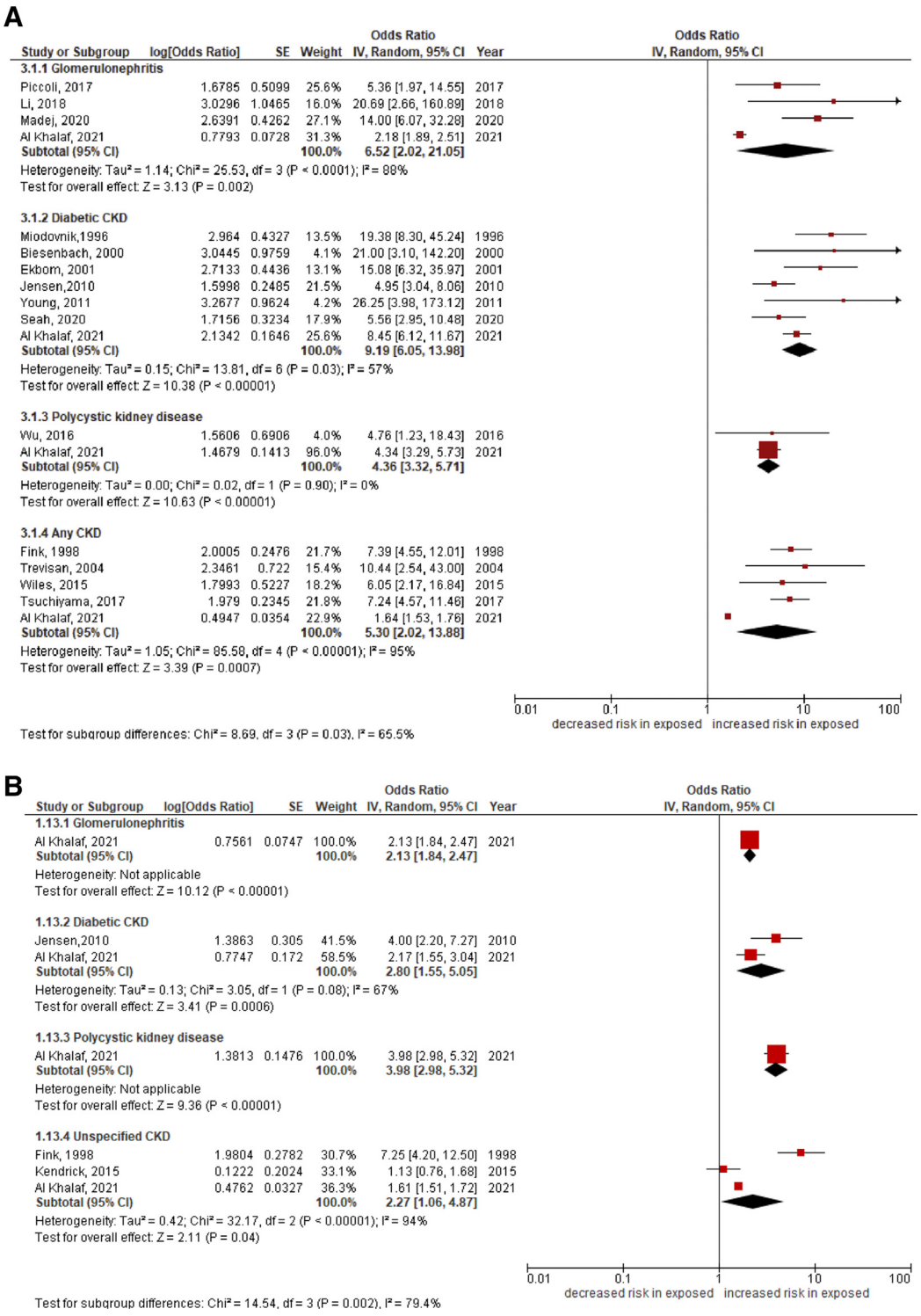


CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

Forest plots of the effect of cause of chronic kidney disease on adverse pregnancy outcomes (compared with no chronic kidney disease).

SUPPLEMENTAL FIGURE 19
Forest plots

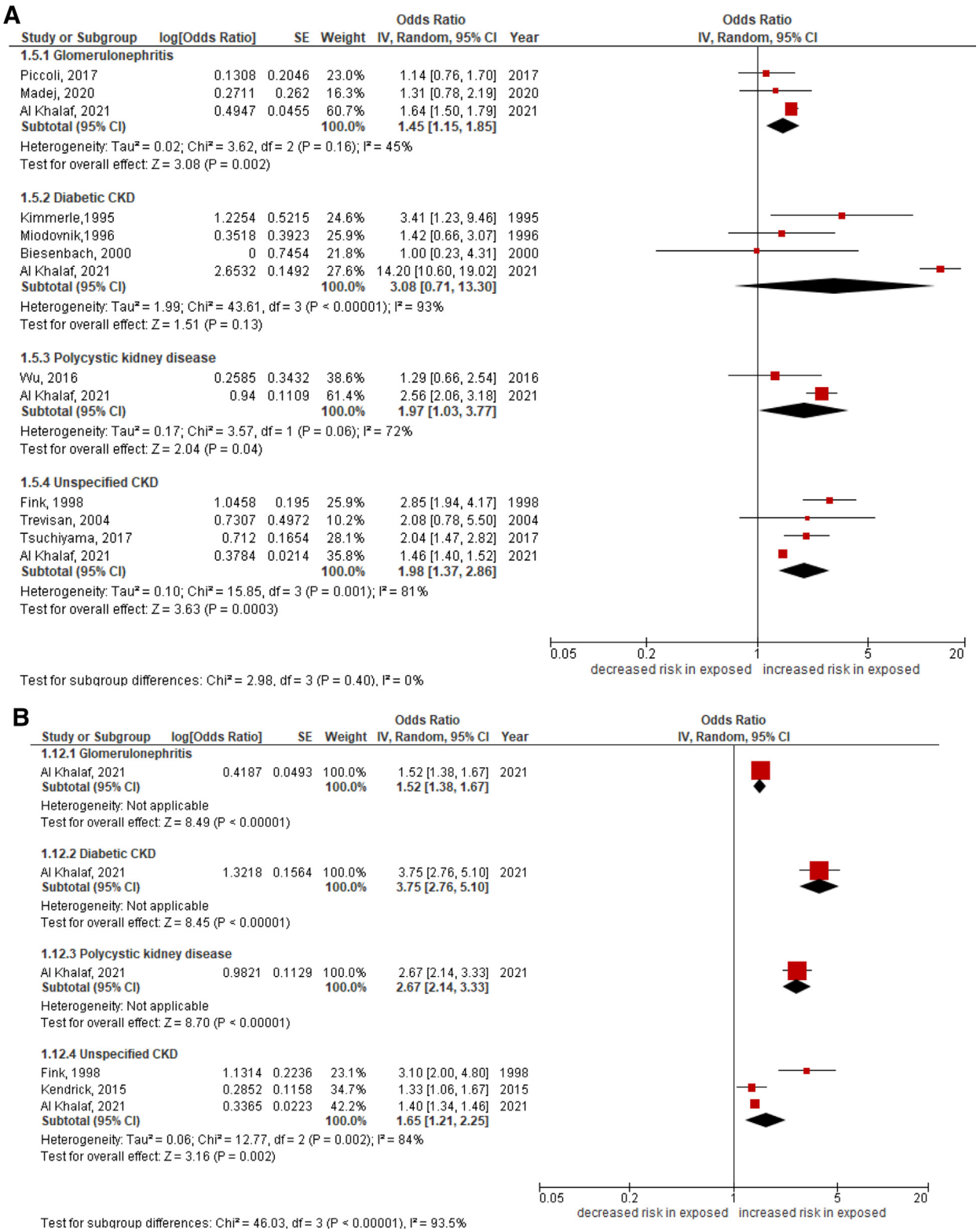


Forest plots of (**A**) crude estimates for preeclampsia and (**B**) adjusted estimated for preeclampsia.

CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 20
Forest plots

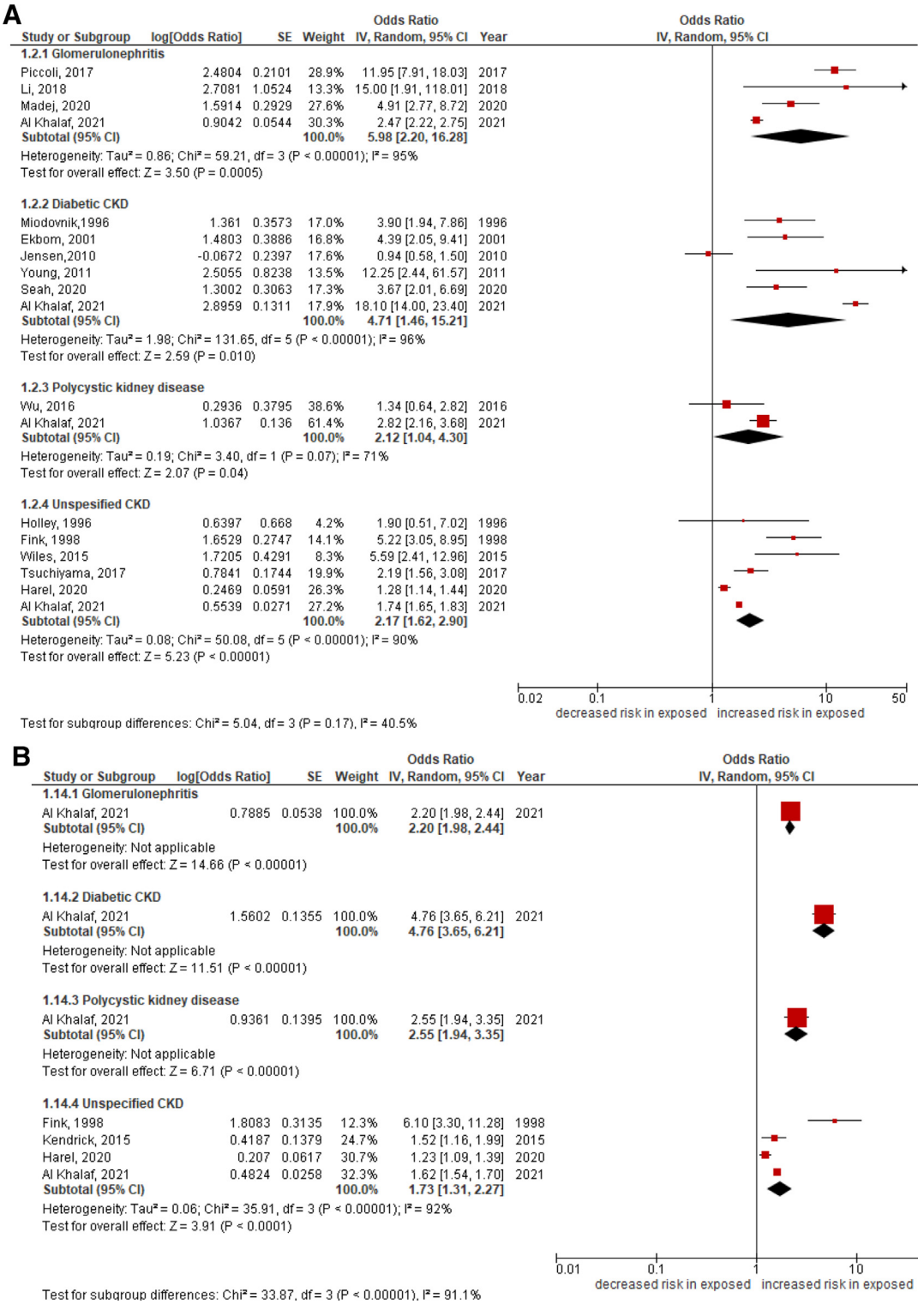


Forest plots of (**A**) crude estimates for CD and (**B**) adjusted estimates for CD.

CI, confidence interval; *CD*, cesarean delivery; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 21
Forest plots

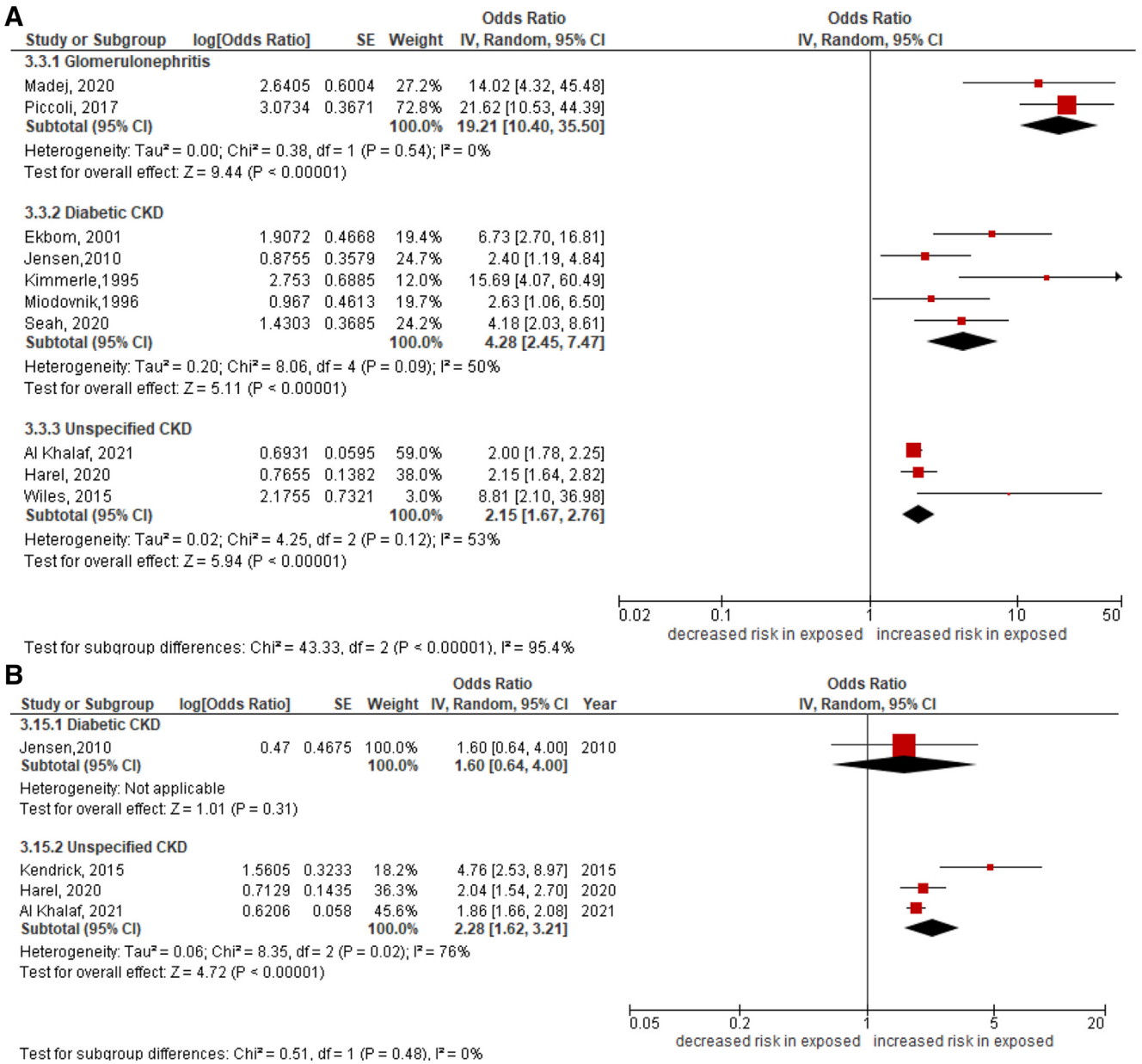


Forest plots of (**A**) crude estimates for preterm birth (<37 weeks' gestation) and (**B**) adjusted estimates for preterm birth (<37 weeks' gestation).

CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 22
Forest plots



Forest plots of (**A**) crude estimates for VPTB (<34 weeks' gestation) and (**B**) adjusted estimates for VPTB (<34 weeks' gestation).

CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error; *VPTB*, very preterm birth.

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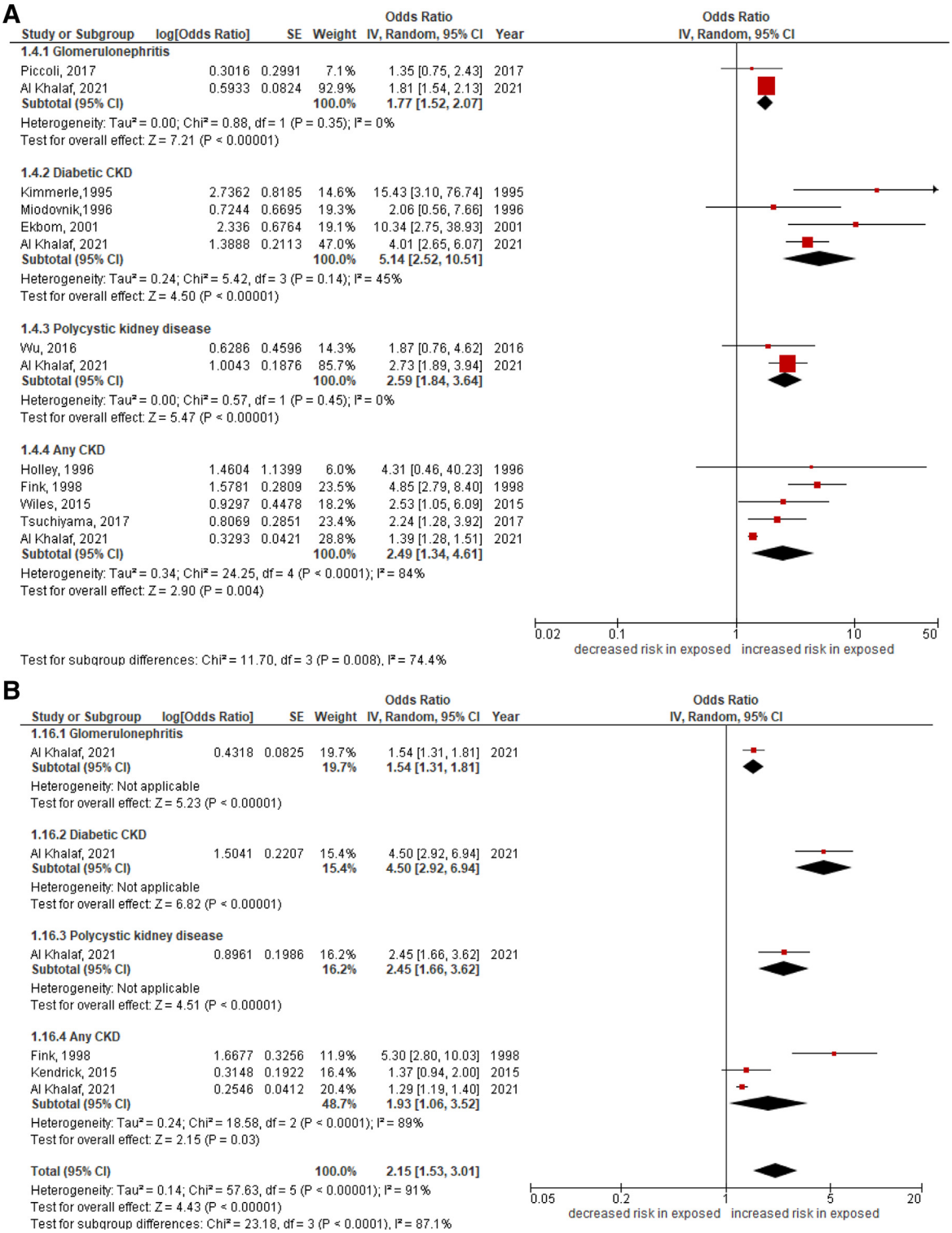
SUPPLEMENTAL FIGURE 23
Forest plots



Forest plots of (**A**) crude estimates for SGA and (**B**) adjusted estimates for SGA.

CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error; *SGA*, small for gestational age.

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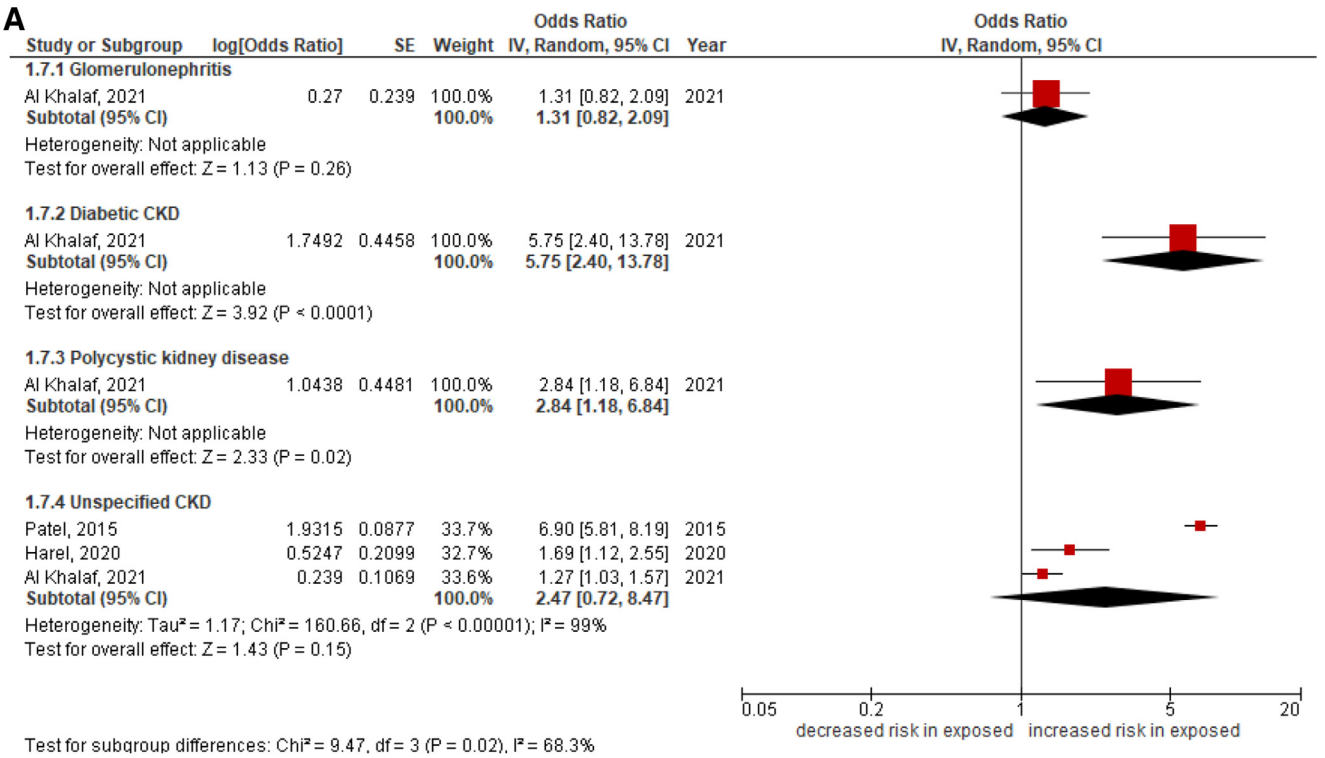
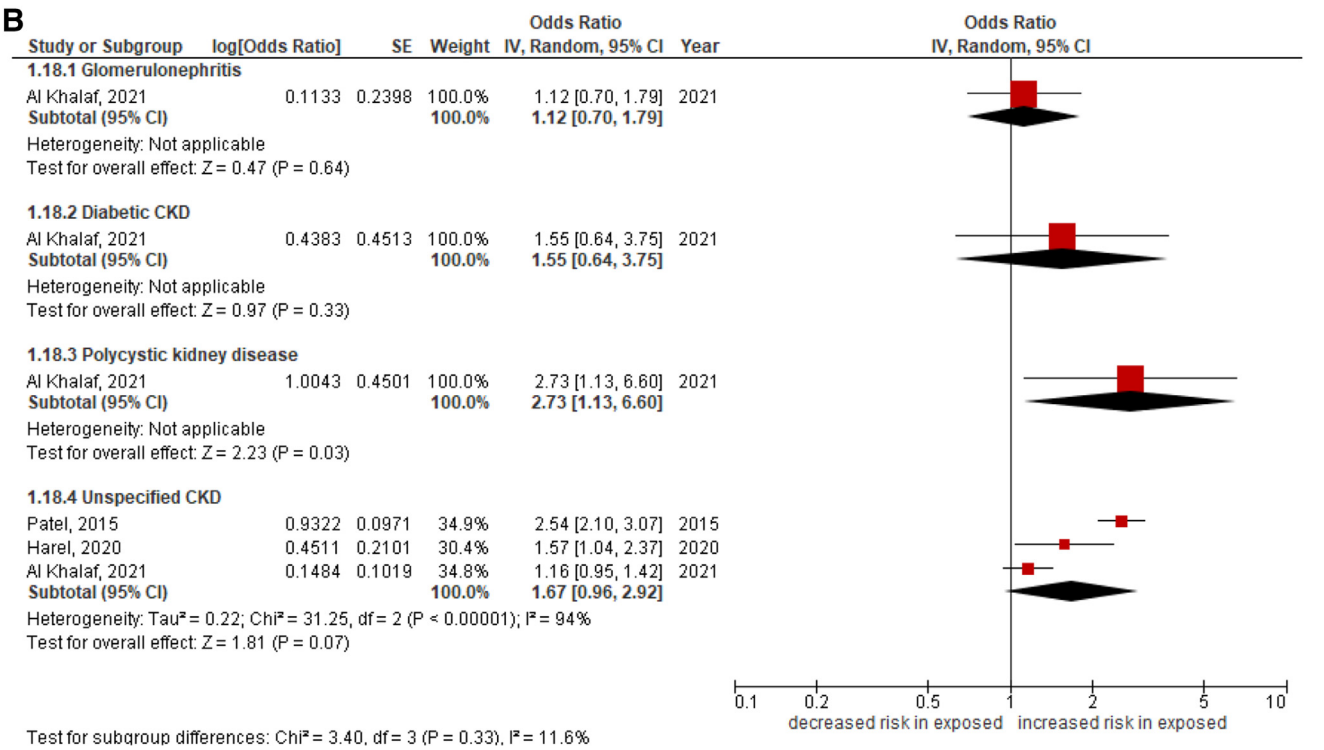
SUPPLEMENTAL FIGURE 24
Forest plots





Forest plots of (**A**) crude estimates for stillbirth and (**B**) adjusted estimates for stillbirth.

CI, confidence interval; *CKD*, chronic kidney disease; *IV*, inverse variance; *SE*, standard error.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL TABLE 1

Study characteristics (studies reported the adverse pregnancy outcomes in women with chronic kidney disease vs those without)

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Kimmerle et al[32] 1995	Germany	Prospective cohort	46	DN defined as proteinuria >400 mg/d, creatinine clearance <80 mL/min, and hypertension in the first trimester.	1982–1992	Preeclampsia defined as acute worsening hypertension (>15% diastolic BP) in the presence of proteinuria, CD (not defined).	SGA defined as birthweight lower than 10th percentile, intrauterine/ perinatal deaths (not defined).	None	5[a]
Holley et al,[34] 1996	United States	Prospective cohort	86	Proteinuria ≥150 mg/24 h, or first trimester Sr Cr. 0.8 mg/dL in the first trimester, or proteinuria ≥300 mg/24 h, with known kidney disease.	1991–1993	Spontaneous abortion not defined	Preterm birth defined as birth ≤36 wk of gestation. IUGR, neonatal death, intrauterine fetal death (not reported).	Maternal age, parity, race, and insulin- dependent DM	4[a]
Miodovnik et al[31] 1996	United States	Prospective cohort	182	DN defined as total protein excretion rate: >500 mg/d, or persistent positive albuminuria (dipstick ≥2) in the absence of bacteriuria.	1978–1991	Preeclampsia defined as pregnancy-induced hypertension with proteinuria >500 mg/d in a patient without nephropathy	Preterm birth defined as delivery before 37 complete weeks of gestation, IUGR/SGA defined as birthweight <10th percentile, stillbirth and neonatal mortality.	None	5–6[a]
Fink et al[20] 1998	United States	Retrospective cohort	675	CKD defined according to ICD-9 codes including diabetic and hypertensive nephropathy, acute and chronic glomerulonephritis, nephrotic syndrome, acute and chronic renal failure, disorders with impaired renal function, small kidneys of unknown cause, renal agenesis, and cystic diseases.	1987–1993	Preeclampsia, CD (outcomes not defined)	Neonatal mortality (defined as infant death within 28 d of birth), Preterm birth, SGA, Preterm birth, IUGR.	Maternal age, trimester of first prenatal visit, parity, smoking and chronic hypertension	8[a]
Biesenbach et al[30] 2000	Austria	Prospective cohort	40	Preconceptional persistent macroproteinuria (>0.5 g protein/24 h urine) without UTI and other renal diseases.	1985–1993	CD, preeclampsia (outcomes not defined)	Preterm birth defined as premature delivery (<34 wk of gestation), SGA (2400 g birthweight).	None	6[a]

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

(continued)

SUPPLEMENTAL TABLE 1

Study characteristics (studies reported the adverse pregnancy outcomes in women with chronic kidney disease vs those without) *(continued)*

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Ekbom et al[29] 2001	Denmark	Prospective cohort	240	Micro-albuminuria: 30 −300 mg/24 h; or diabetic nephropathy: >300 mg/24 h.	1996−1999	Miscarriage <22 wk, Preeclampsia defined BP > 140/90 mm Hg accompanied by proteinuria.	Preterm delivery (<37 wk Of gestation) SGA <10th percentile perinatal mortality defined fetal death later than 22 wk.	None	7[a]
Trevisan et al[28] 2004	Brazil	Retrospective cohort	75	CRI defined as Sr. Cr >1.5 mg/dL	1989−1999	Preeclampsia, CD.	Preterm birth; delivery for 28−36 wk, Stillbirth (abortion; pregnancy that last for 20−28 wk).	Maternal and gestational age, time of delivery	5[a]
Jensen et al[27] 2010	Denmark	Prospective Cohort	846	Microalbumin in early pregnancy defined as UAER between 30 and 300 mg/24 h or between 20 and 200 ug/min.	1993−1999	Preeclampsia defined as BP >140/90 mm Hg.	Preterm birth defined as delivery before 37 gestational wk, SGA, birthweight.	Age, BMI, duration of diabetes, parity, prepregnancy insulin dosage, blood pressure ≥140/90 mm Hg at first visit, proliferative retinopathy, first/third trimester A1C.	8[a]
Young et al[26] 2011	Brazil	Prospective cohort	43	DN defined by the criteria of NKF.	2010−2011	Preeclampsia (not defined)	Preterm birth defined as prematurity <37 wk, LBW defined as <2500 g or 10th percentile for gestational age, fetal death defined as death after 22 wk, stillbirth defined as expulsion of fetus <500 g.	None	6[a]
Davidson et al[47] 2015	Australia	Retrospective cohort	62,357	CKD defined using the KDOQI guidelines.	2003−2010	Preeclampsia and Hypertension in pregnancy were defined according to both SOMANZ and ISSHP guidelines	Preterm birth defined as birth in which a child is delivered before it reached the full of gestation (37 wk). SGA defined as birthweight, length, or head circumference below the 10th percentile for gestational age. IUGR defined as birthweight below the 10th percentile for gestational age.	None	5−6[a]

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 1

Study characteristics (studies reported the adverse pregnancy outcomes in women with chronic kidney disease vs those without) *(continued)*

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Kendrick et al[25] 2015	United States	Retrospective cohort	1156	ICD-P code/ NKF-KDOQI, GFR <60 mL/ min / 1.73 m^2 for >3 mo or Sr. Cr >1.2 mg/ dL in first trimester.	2000–2013	CD, Preeclampsi, maternal death defined as death occurring at any time.	Preterm birth defined as <37 wk gestation, LBW defined as <2500, SGA defined as <10th percentile of birthweight, NICU admission and fetal death defined as death during hospitalization.	Age, race, history of diabetes, chronic hypertension, liver disease, connective tissue disease to women without CKD.	8[a]
Patel et al[24] 2015	United States	Prospective cohort	12,524,119	ICD-9 coding	2000–2010	Maternal outcomes definition not reported	Fetal outcomes definition not reported.	Age, race/ethnicity, insurance, multiple gestation, diabetes, chronic hypertension, diabetes with chronic hypertension, cardiomyopathy, congenital heart disease, cardiac conduction disorders, systemic lupus erythematous, collagen vascular disease, HIV, thrombophilia/APS, sickle cell disease/trait, drug use, alcohol use, tobacco use, gestational diabetes, preeclampsia/eclampsia, fetal growth restriction, placental abruption	8[a]
Wiles et al[44] 2015	United Kingdom	Retrospective cohort	312	CKD definition not reported.	2003–2011	Preeclampsia not defined; documented diagnosis in the hospital database.	Fetal growth restriction <10th percentile for gestational age. Preterm birth delivery defined as birth <37 wk of gestation. Intrauterine death defined as death >24 wk of gestation. Pregnancy loss defined as second trimester miscarriage or intrauterine death.	None	5[a]

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

(continued)

SUPPLEMENTAL TABLE 1

Study characteristics (studies reported the adverse pregnancy outcomes in women with chronic kidney disease vs those without) *(continued)*

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Wu et al[23] 2016	United States	Cohort study	146	Diagnosis of ADPKD was determined by ultrasound using the following criteria: patients <30 y: at least 2 cysts in 1 kidney or 1 cyst in each kidney; patients aged 30–59 y: at least 2 cysts in each kidney and patients aged ≥ 60 y: at least 4 cysts in each kidney.	1975–2010	Preeclampsia defined as new-onset hypertension sBP 140 mm Hg or dBP 90 mm Hg measured on 2 occasions, 6 h apart) and proteinuria 300 mg in a 24-h urine specimen after 20 wk of gestation	SGA/IUGR defined as weight >10th percentile for gestational age, Premature delivery (delivery before the 37th gestational wk or 259 d from the first day of the last menstrual period). Neonatal death (death within the first month of life). Abortion defined as elective, therapeutic or spontaneous fetal loss before 20 wk of gestation. Stillborn defined as birth of a nonviable fetus after 20 wk of gestation.	None	7[a]
Piccoli et al[46] 2017	Italy	Prospective cohort	1544	GN defined according to KDOQI guidelines (CKD-EPI formula).	Not Reported	CD, Preeclampsia defined as hypertension accompanied by proteinuria after 20 wk gestational in a previously normotensive, nonproteinuric woman.	Preterm birth defined as birth <37 wk, VPTB defined as birth <34 wk, SGA defined as birthweight below the 10th percentile.	CKD stage, age, nulliparous race, referral proteinuria, hypertension	6–7[a]
Tsuchiyama et al[22] 2017	Japan	Retrospective cohort	3206	CKD was diagnosed on the basis of the KDOQI definition of CKD.	2001–2010	Preeclampsia defined as hypertension >140/90 mm Hg accompanied by proteinuria after the 20th wk of gestation	Threatened preterm labor defined as progressive dilation of the cervix combined with regular uterine contractions that occurred between 22 and 36 wk of gestation. SGA (below the 10th birthweight percentile for the infant's gestational age). Neonatal death defined as death within 28 d of birth.	None	7[a]

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 1

Study characteristics (studies reported the adverse pregnancy outcomes in women with chronic kidney disease vs those without) *(continued)*

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Li et al[21] 2018	China	Retrospective cohort	114	CGN defined according to KDOQI guidelines. Urine protein >0.5 g/d.	2018	Preeclampsia defined by onset of BP >110 mm Hg	Preterm birth defined as Premature, SGA defined as birthweight <10th percentile, LBW <2500 g, IUGR fetal growth curve below 10th percentile, Fetal loss defined as abortion because of the disease.	None	5[a]
Harel et al[35] 2020	Canada	Population-cohort based	55,964	serum creatinine >95th percentile (ie, >77 μmol/L).	2007–2016	None	Preterm birth defined as gestational age <37 wk, very defined as gestational age <32 wk, stillbirth ≥20 wk gestation.	Maternal age, rural or urban residence, residential income, region of origin, diabetes mellitus, chronic hypertension, and illicit drug or tobacco use within 4 y before the index conception date.	8[a]
Madej et al[45] 2020	Poland	Retrospective cohort	387	Biopsy-proven GN. CKD stage was classified as follows: CKD1: eGFR >90; CKD2: eGFR 89–60; CKD3: eGFR 59–30, and CKD4: eGFR 15–29 mL/min/1.73 m^2, according to the KDIGO.	2013–2018	Preeclampsia defined as new-onset hypertension and proteinuria with protein excretion >0.3 g/d after 20 wk of gestation in women without underlying hypertension and proteinuria, new-onset hypertension and doubling of daily proteinuria after 20 wk of gestation in women without hypertension but with proteinuria (with protein excretion >0.3 g/24 h at baseline), and either worsening hypertension or doubling of proteinuria in women with both hypertension and proteinuria (with protein excretion >0.3 g/24 h at baseline).	Preterm birth defined as gestational age <37 wk Stillbirth defined as death after 21 wk Of gestation, Neonatal death defined as live-born infant dying within 28 d of delivery.	None	7[a]

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 1

Study characteristics (studies reported the adverse pregnancy outcomes in women with chronic kidney disease vs those without) *(continued)*

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Seah et al,[33] 2020	Australia	Prospective cohort	307	eGFR was calculated on the basis of the CKD-EPI formula. Stages of diabetic kidney disease was defined according to the KDIGO guidelines and hyperfiltration define as an eGFR >120 mL/min/1.73 m^2, microalbuminuria was defined as urinary albumin excretion of 30–300 mg/d or urinary ACR of 3.5 to 35.0 mg/mmol. Macroalbuminuria was defined as urinary albumin excretion >300 mg/d or urinary ACR >35.0 mg/mmol.	2004-2014	Preeclampsia defined as the development of sBP >140 mm Hg±dBP >90 mm Hg, and proteinuria > 300 mg/24 h after 20 wk gestation and clinical diagnosis.	Preterm birth defined as delivery <37 wk of gestation with no separation made between iatrogenic and spontaneous. NICU (no definition reported).	None	6[a]
Al Khalaf et al[36] 2021	Sweden	Retrospective cohort	2784 490	ICD8–ICD10 codes	1982–2012	Preeclampsia defined as at least 2 dBP≥90 mm Hg, combined with proteinuria (≥0.3 g/d or ≥1+ on a urine dipstick), CD.	Preterm birth defined as gestational age <37 wk, very defined as gestational age <32 wk, stillbirth defined as fetal loss >28 wk (until June 2008) or > 22 wk (since July 2008), SGA defied as a birthweight below 2 SDs of the mean birthweight.	Adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), birth year, and child's sex.	8[a]

ACR, albumin-creatinine ratio; *APS*, antiphospholipid syndrome; *ADPKD*, autosomal dominant polycystic kidney disease; *BMI*, body mass index; *CGN*, chronic glomerular-nephritides; *CKD*, chronic kidney disease; *CKD- EPI*, chronic kidney disease epidemiology collaboration; *CRI*, chronic renal insufficiency; *DM*, diabetes mellitus; *DN*, diabetic nephropathy; *eGFR*, estimated glomerular filtration Rate; *GFR*, glomerular filtration rate; *HCPA*, Hospital the Clinicas of Porto Alegre-Brazil; *ICD*, International Classification of Diseases; *IUGR*, intrauterine growth retardation/restriction; *KDIGO*, kidney disease: improving global outcomes; *KDOQI*, kidney disease outcomes quality initiative; *LBW*, low birthweight; *NICU*, neonatal intensive care unit/ need for intensive care unit; *SD*, standard deviation; *SGA*, small for gestational age; *UAER*, urinary albumin excretion rate; *UTI*, urinary tract infection.

[a] Values between 0–3 stars are considered as low quality, 4–6 stars as moderate quality and 7–9 stars as high quality.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL TABLE 2

Study characteristics (studies reported the adverse pregnancy outcomes in women with late stages compared with early stages of chronic kidney disease)

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study Year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Reece et al[41] 1988	United States	Retrospective cohort	31	DN defined as urinary protein level was ≥300 mg/24 h before the third trimester. The severity of the proteinuria was categorized as mild (300 to 499 mg/24 h), moderate (500 to 3000 mg/24 h), and severe or nephrotic syndrome (>3 gm/24 h).	1975–1984	Preeclampsia defined acute worsening of BP (>15% increase in sBP or dBP or deterioration of renal function associated with multisystemic involvement, result-ting in abnormal liver function and coagulation studies, particularly elevation in the fibrin split products and thrombocytopenia.	Not reported	None	5-6[a]
Imbasciati et al[40] 2007	Italy	Cohort study	49	GFR was estimated using the Modification of Diet in Renal Disease 4-variable equation (on the basis of serum creatinine level, age, sex, and race) and expressed in mm per minute per 1.73 m^2 of body surface area.	1977–2004.	CD (not reported)	Preterm delivery defined as (live birth before the 37th wk), stillbirth (intrauterine death after 24 wk of gestation), neonatal death (live infant dying within 28 d after delivery), and perinatal death (obtained as the sum of stillbirths and neonatal deaths). SGA (infants with birthweight >10th percentile of the Italian population according to gestational week at delivery. LBW (live-born infant weighing <2500 g).	None	7[a]

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

(continued)

SUPPLEMENTAL TABLE 2

Study characteristics (studies reported the adverse pregnancy outcomes in women with late stages compared with early stages of chronic kidney disease) *(continued)*

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study Year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Bramham et al[11] 2011	United Kingdom and Netherlands	Prospective cohort	36	Mild CKD and moderate/ severe CKD were defined as prepregnancy Cr<125 mmol/L and Cr>125 mmol/L, respectively.	2003–2005	Preeclampsia was defined as the new development of proteinuria in accordance with the ISSHP.	SGA defined as birthweight <10th percentile. Preterm birth (37 wk and <34 wk gestation). Perinatal death (intrauterine >24 wk gestation or postnatal by 7 d). NICU (not defined).	None	6[a]
Davidson et al[47] 2015	Australia	Retrospective cohort	55	CKD defined using the KDOQI guidelines.	2003–2010	Preeclampsia and Hypertension in pregnancy were defined according to both SOMANZ and ISSHP guidelines.	Preterm birth defined as birth in which a child is delivered before it reached the full of gestation (37 wk). SGA defined as birthweight, length, or head circumference below the 10th percentile for gestational age. IUGR defined as birthweight below the 10th percentile for gestational age.	None	5–6[a]
Feng et al[10] 2015	United States	Retrospective cohort	41	Severe CKD defined as estimated GFR (eGFR) <30 mL/min within the first 3 mo of pregnancy. Mild CKD defined as estimated GFR (eGFR) 45–100 mL/min.	2000–2012	Preeclampsia defined as blood pressure >140/90 mm Hg and 2+ proteinuria on dipstick after second trimester.	Prematurity was defined as birth before 37 wk of gestation. Perinatal death was defined as newborn death <4 wk of age. Low birthweight was defined as <2500 g.	None	6–7[a]
Singh et al[39] 2015	India	Retrospective cohort	51	CKD defined by KDOQI guidelines abnormality.	2009–2012	Not reported	Not reported	None	7[a]

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 2

Study characteristics (studies reported the adverse pregnancy outcomes in women with late stages compared with early stages of chronic kidney disease) *(continued)*

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study Year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Wiles et al[44] 2015	United Kingdom	Retrospective cohort	35	CKD definition not reported.	2003–2011	Preeclampsia not defined; documented diagnosis in the hospital database.	Fetal growth restriction <10th percentile for gestational age. Preterm birth delivery defined as birth <37 wk of gestation. Intrauterine death defined as death >24 wk of gestation. Pregnancy loss defined as second trimester miscarriage or intrauterine death.	None	5[a]
Bharti et al[38] 2016	India	Retrospective cohort	80	CKD is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 mo (CKD definition according to NKF-KDOQI guidelines).	2005–2015	Preeclampsia defined as new-onset hypertension after 20 wk Of pregnancy associated with proteinuria, CD (not defined).	SGA defined as infants <10th percentile, preterm birth (<37 wk gestation), NICU, stillbirths,	None	7[a]
Piccoli et al[46] 2017	Italy	Prospective cohort	126	GN defined according to KDOQI guidelines (CKD-EPI formula).	Not Reported	CD, Preeclampsia.	Preterm birth, VPTB, SGA,	CKD stage, age, nulliparous race, referral proteinuria, hypertension	6–7[a]
He et al[37] 2018	China	Retrospective cohort	293	CKD defined on the basis of a history of CKD, clinical examination, renal function tests, 24-h urinary protein excretion, renal ultrasound, and renal biopsy. The staging of kidney diseases was based on the eGFR level.	2005–2016	Preeclampsia defined on the basis of 2013 Hypertension in Pregnancy Guidelines of ACOG.	Preterm birth defined as gestational age at birth of <34 wk. LBW defined as neonatal birthweight ≤1500 g.	None	6–7[a]

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 2

Study characteristics (studies reported the adverse pregnancy outcomes in women with late stages compared with early stages of chronic kidney disease) *(continued)*

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study Year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Leaños-Miranda et al[9] 2019	Mexico	Cohort study	167	CKD stage was defined according to KDIGO guidelines. GFR was calculated using the CKD-EPI formula on the basis of preconception data or serum creatinine measured at first control in pregnancy.	2011–2017	Preeclampsia defined according to The American College of Obstetricians and Gynecologists criteria.	Preterm delivery (<34 wk of gestational age). Stillbirths defined as death of a fetus. Neonatal death defined as death of a newborn until hospital discharge and SGA defined as an infant whose birthweight was <10th percentile.	Proteinuria, urinary IgM, CKD stages, and chronic hypertension	8[a]
Madej et al[45] 2020	Poland	Retrospective cohort	72	Biopsy-proven GN. CKD stage was classified as follows: CKD1: eGFR >90; CKD2: eGFR 89–60; CKD3: eGFR 59–30, and CKD4: eGFR 15–29 mL/min/1.73 m^2, according to the KDIGO.	2013–2018	Preeclampsia defined as new-onset hypertension and proteinuria with protein excretion >0.3 g/d after 20 wk of gestation in women without underlying hypertension and proteinuria, new-onset hypertension and doubling of daily proteinuria after 20 wk of gestation in women without hypertension but with proteinuria (with protein excretion >0.3 g/24 h at baseline), and either worsening hypertension or doubling of proteinuria in women with both hypertension and proteinuria (with protein excretion >0.3 g/24 h at baseline).	Preterm birth defined as gestational age <37 wk Stillbirth defined as death after 21 wk of gestation, Neonatal death defined as live-born infant dying within 28 d of delivery.	None	7[a]

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

(continued)

SUPPLEMENTAL TABLE 2

Study characteristics (studies reported the adverse pregnancy outcomes in women with late stages compared with early stages of chronic kidney disease) *(continued)*

Study, Year	Country	Study design	Sample size	Definition of chronic kidney disease	Study Year	Defined maternal outcomes	Defined fetal outcomes	Variable accounted for	Quality assessment
Wiles et al[42] 2020	United Kingdom	Retrospective cohort	178	eGFR<60 mL/min/ 1.73 m^2, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. OR a creatinine >125 mmol/L before 20 wk gestation in the absence of a precipitant for kidney injury.	2003 and 2017	CD.	SGA defined as birthweight<10th percentile, preterm birth (<37 wk gestation), VPTB (<34 wk) and NICU admission.	None	6[a]
Madazli et al[43] 2021	Turkey	Retrospective cohort	101	CKD defined as kidney damage (albumin-to-creatinine ratio >30 mg/ 24 h 2 of 3 urine specimens, urine sediment abnormalities, tubular disorders, histologically diagnosed abnormalities, structural abnormalities detected by scanning) OR GFR<60 mL/min/ 1.73 m^2 for 3 mo on the basis of KDIGO guidelines.	2009 and 2019	Preeclampsia defined according to ACOG guidelines; superimposed preeclampsia was defined as CKD with hypertension with new onset or sudden increase in proteinuria, sudden increase in BP, thrombocytopenia or deranged liver or kidney function.	stillbirth defined as fetal death after 22 wk, neonatal death that occurred <28 d after birth, perinatal death (stillbirth+neonatal death), SGA defined as slowing of fetal growth velocity during ≥2 consecutive ultrasound with measurements ≥3 wk apart and fetal abdominal circumference <2 SD for gestational age)	None	7[a]

ACOG, American College of Obstetricians and Gynecologists; *CD*, cesarean delivery; *CKD*, chronic kidney disease; *dBP*, diastolic blood pressure; *DN*, diabetic nephropathy; *eGFR*, estimated glomerular filtration rate; *GFR*, glomerular filtration rate; *ISSHP*, International Society of Study of Hypertension in Pregnancy; *IUGR*, intrauterine growth retardation/restriction; *KDIGO*, kidney disease, improving global outcomes; *KDOQI*, kidney disease outcomes quality initiative; *LBW*, low birthweight; *MAP*, mean arterial pressure; *MDRD*, modification of diet in renal disease; *NICU*, neonatal intensive care unit/ need for intensive care unit; *NKF*, National Kidney Foundation; *PCR*, protein creatine ratio; *PE*, preeclampsia; *sBP*, systolic blood pressure; *SGA*, small for gestational age; *SD*, standard deviation; *SOMANZ*, Society of Obstetric Medicine of Australia and New Zealand; *TOCOS*, Torino Cagliari Observational study.

[a] Values between 0–3 stars are considered as low quality, 4–6 stars as moderate quality and 7–9 stars as high quality.

Al Khalaf. Chronic kidney disease and adverse pregnancy outcomes. Am J Obstet Gynecol 2022.

SUPPLEMENTAL TABLE 3

Sensitivity analyses of the associations between chronic kidney disease and adverse pregnancy outcomes (by location and decade of publication)

		Crude estimates				Adjusted estimates[a]			
Outcomes	Subgroup	Number of studies	OR, 95% CI	I^2 (%)	Test for subgroup differences (*P* value)	Number of studies	OR, 95% CI	I^2 (%)	Test for subgroup differences (*P* value)
Preeclampsia									
Location	Asia	2	7.61 (4.86–11.9)	0	.63	—	—	—	
	Australia	1	5.56 (2.95–10.5)	—		—	—	—	
	Europe	7	6.70 (2.80–16.0)	93		2	2.41 (0.99–5.85)	89	.88
	North America	3	9.33 (4.49–19.4)	57		2	2.83 (0.46–17.5)	97	
	South America	2	14.6 (4.69–45.2)	0		—	—	—	
Year of publication	Publication ≤2010	6	9.69 (5.90–15.9)	55	.42	2	5.45 (3.05–9.76)	52	
	Publication >2010	9	6.63 (3.07–14.32)	92		2	1.43 (1.03–1.98)	66	<.0001
Cesarean delivery									
Location	Asia	1	2.04 (1.47–2.82)	—	.19	—	—	—	.002
	Australia	—	—	—		—	—	—	
	Europe	5	1.43 (1.24–1.64)	11		1	1.40 (1.34–1.46)	—	
	North America	3	1.86 (1.06–3.27)	63		2	1.99 (0.87–4.55)	91	
	South America	1	2.08 (0.78–5.50)	—		—	—	—	
Year of publication	Publication ≤2010	5	2.33 (1.65–3.30)	10	.02	1	3.10 (2.00–4.80)	—	.0004
	Publication >2010	5	1.48 (1.26–1.73)	31		2	1.40 (1.34–1.46)	0	
Preterm birth (<37 wk)					.45				
Location	Asia	2	4.33 (0.71–26.31)	69		—	—	—	.44
	Australia	1	3.67 (2.01–6.69)	—		—	—	—	
	Europe	6	3.58 (1.63–7.85)	96		1	1.62 (1.54–1.70)	—	
	North America	5	2.32 (1.14–4.71)	88		3	2.04 (1.14–3.65)	92	
	South America	1	12.25 (2.44–61.57)	—		—	—	—	
Year of publication	Publication ≤2010	5	2.77 (1.25–6.18)	86	.74	1	6.10 (3.30–11.28)	—	<.0001
	Publication >2010	10	3.21 (2.25–4.60)	92		3	1.44 (1.17–1.78)	88	

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(continued)

SUPPLEMENTAL TABLE 3

Sensitivity analyses of the associations between chronic kidney disease and adverse pregnancy outcomes (by location and decade of publication)

(continued)

		Crude estimates				Adjusted estimates[a]			
Outcomes	**Subgroup**	**Number of studies**	**OR, 95% CI**	**I^2 (%)**	**Test for subgroup differences (*P* value)**	**Number of studies**	**OR, 95% CI**	**I^2 (%)**	**Test for subgroup differences (*P* value)**
VPTB (<34 wk)									
Location	Asia	—	—	—	.02	—	—	—	—
	Australia	1	4.18 (2.03–8.61)	—		—	—	—	—
	Europe	7	7.05 (2.87–17.36)	91		2	1.86 (1.66–2.08)	0	.27
	North America	2	2.19 (1.69–2.83)	0		2	4.76 (2.53–8.97)	—	
	South America	—	—	—		—	—	—	
Year of publication	Publication ≤2010	4	4.49 (2.09–9.62)	63	.80	1	1.60 (0.64–4.00)	—	.48
	Publication >2010	6	5.09 (2.76–9.37)	91		3	2.28 (1.62–3.21)	76	
Small for gestational age									
Location	Asia	1	2.24 (1.28–3.92)	—	.65	—	—	—	.29
	Australia	—	—	—		—	—	—	
	Europe	5	2.69 (1.37–5.28)	79		1	1.29 (1.19–1.40)	—	
	North America	4	3.25 (1.87–5.65)	22		2	2.63 (0.70–9.88)	92	
	South America	—	—	—		—	—	—	
Year of publication	Publication ≤2010	5	5.37 (3.07–9.39)	17	<.0001	1	5.30 (2.80–10.03)	—	<.0001
	Publication >2010	5	1.53 (1.25–1.87)	18		2	1.29 (1.20–1.40)	0	

CI, confidence interval; *OR*, odds ratio; *VPTB*, very preterm birth.

[a] For adjusted estimates we followed the author's definitions.

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