A systematic review and meta-analysis indicates long-term risk of chronic and end-stage kidney disease after preeclampsia

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Preeclampsia is a pregnancy-related syndrome of variable severity, classically characterized by acute kidney involvement, with hypertension and/or proteinuria and reduced kidney function. Once considered a self-limited disease healed by delivery, it is now acknowledged that preeclampsia can affect cardiovascular and kidney health in the long term. The entity of risk has not been established and consequently follow-up policies have not been defined. Here we undertook a systematic review to gain better insights into the need for post–preeclampsia follow-up. Articles published between January 2000 and March 2018 were selected, dealing with at least 20 preeclampsia patients, with follow-up of 4 years or more (MEDLINE, Embase, and Cochrane Library). No quality selection or language restriction was performed. Of the 10,510 titles and abstracts originally considered, 21 papers were selected, providing information on 110,803 cases with and 2,680,929 controls without preeclampsia, with partial overlap between studies on the same databases. Heterogeneity was high, and a random meta-analytic model selected. The increase in risk of end stage renal disease after preeclampsia was significant (meta-analytic risk ratios (95% confidence interval) 6.35 (2.73-14.79)); the risk of albuminuria and chronic kidney disease increased but statistical significance was not reached (4.31 (0.95-19.58) and 2.03 (0.58-7.32), respectively). Translating meta-analytic risk into the number of patients who need follow-up to detect one adverse event, 310 patients with preeclampsia are needed to identify one woman with end stage renal disease or four to identify one woman with albuminuria. Heterogeneity in definitions, insufficient follow-up and incomplete recruitment may account for discrepancies. Thus, preeclampsia significantly increases the risk of end stage renal disease. However, there is lack of sufficient data to show a relationship between preeclampsia, albuminuria and chronic kidney disease, underlining the need for further prospective studies.

Preeclampsia (PE) is a pregnancy-related syndrome of variable severity that has been differently defined, pointing to hypertension, fetal growth, and kidney involvement.[1–3] Although the presence of proteinuria, which was long seen as a requisite for diagnosis, is no longer considered to be a condition *sine qua non*, an increase in serum creatinine is presently considered an alternative diagnostic element, thus further pointing to the central role of the kidney in this syndrome.[1–12] PE has in fact been defined as a transitory reversible kidney disease that resolves spontaneously after delivery. In the classical definition of PE, kidney derangements are reversible within 1 to 3 months of delivery, regardless of their severity; however, this may not be the case in all patients, and the relationship between PE and chronic kidney disease (CKD) is not entirely understood.[13–18]

The prevalence of PE has been variously estimated: the range most frequently reported is 3% to 5%, but may decrease to 1% to 2% in "low-risk pregnancies" or increase to >10% if related disorders such as pregnancy-induced hypertension and hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome are included within the broad definition of "the hypertensive disorders of pregnancy." The non-univocal definition of superimposed PE, identifying cases in which the clinical syndrome of hypertension and proteinuria develops in the presence of preexisting hypertension or kidney disease, adds to the difficulty in reaching univocal definitions.[1–4,18–23] The discussion on whether PE is a single disease, a syndrome, or a spectrum of alterations is still open; the new molecular approaches, and in particular the analysis of the ratio between proangiogenic and anti-angiogenic factors, such as placental growth factor and soluble fms-like tyrosine kinase 1, may offer some interesting insights into its pathogenesis.[1–4,21–30]

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PE is no longer considered as a transitory disease and has been associated with a vast array of cardiovascular and renal diseases, of which the pregnancy-related affection may be a herald, a cause, or a consequence.[31–36] Most of the studies and virtually all the systematic reviews show that patients who had PE in ≥1 pregnancy are at an increased risk of developing cardiovascular and metabolic diseases.[31–41] However, the entity of the risk, the timing of the development of clinical problems, and the control strategies that can be used are not clear, and large prospective cohort studies are still lacking.

This uncertainty is shared by the analysis of the risk of CKD (including end-stage renal disease [ESRD]), which may become clinically evident only in the long term and whose global prevalence remains low, possibly too low to justify specific follow-up programs. A comprehensive systematic review focused on kidney disease, performed in 2010, highlighted the association between microalbuminuria (but not estimated glomerular filtration rate [eGFR]) and a previous episode of PE.[42] The review includes 7 studies reporting on outcomes recorded at least 6 weeks postpartum (~300 PE episodes). Several large studies were published after this review appeared, and information is also accumulating on hard outcomes, such as ESRD.

It was in this context that we decided to undertake the present systematic review to gather updated information from large recent observational and cohort studies focused on the long-term occurrence of ESRD, CKD (defined on the basis of glomerular filtration rate [GFR] and presence of proteinuria), and morbidity from kidney-related causes after an episode of PE as a guide for defining long-term control and CKD prevention strategies.

RESULTS
Characteristics of the studies
After removing duplicates, 8366 titles and abstracts were screened and the full texts of 159 articles were assessed, leading to a final selection of 21 articles for qualitative synthesis and 11 included in the different meta-analyses (Figure 1).[43–63]

Overall, qualitative data provided information on 110,803 cases and 2,680,929 controls, with a partial overlap between studies in the same databases (Table 1).

Selected studies were heterogeneous in terms of number of cases (30–26,651), setting of the study, over half being from European countries, period of pregnancy, and duration of follow-up (Table 1).

None of the studies were prospective; the interval between pregnancy and analysis ranged from 4.4 to >30 years. The definition of exposure (PE alone or combined with other hypertensive disorders of pregnancy) and the definitions of the outcomes and their measures were not homogeneous,
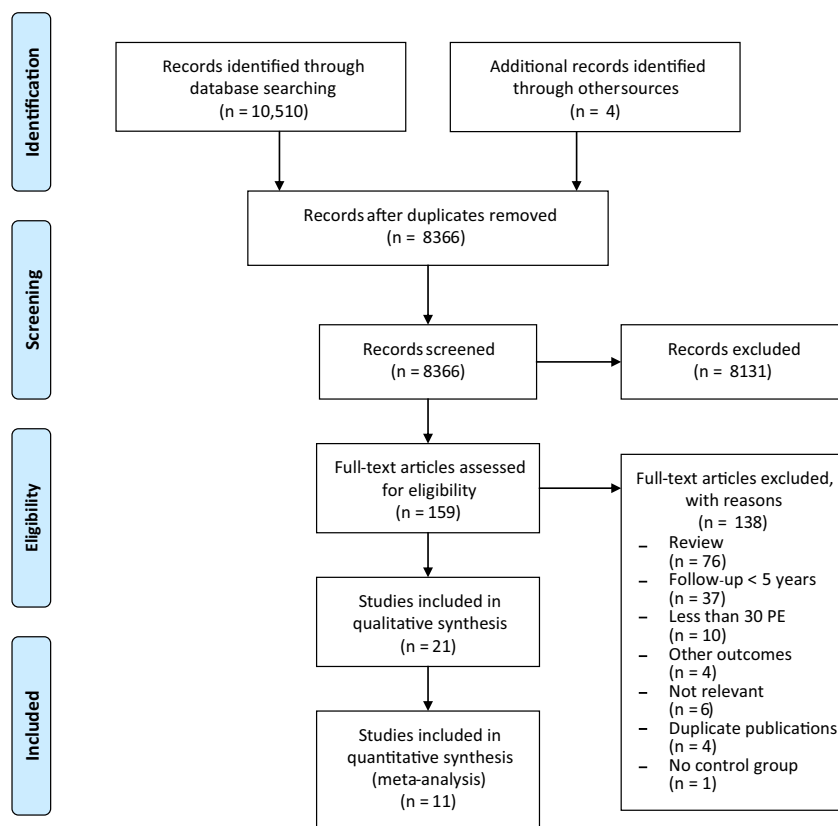

Figure 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection and database search. PE, preeclampsia. Reprinted with permission from Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097. Copyright © 2009 Moher *et al.*

following also the changes that have occurred over time in the nomenclature of these diseases (Tables 2[64] and 3).

There were 2 main types of study design: cross-sectional evaluation of a cohort of patients retrospectively identified (8 studies) and linkage between different databases (11 studies). Two studies analyzed selected patients using questionnaires administered in the setting of a randomized controlled trial for other purposes (Table 2).

Four main outcomes were examined, alone or in combination: development of ESRD (Table 4), GFR level or presence of CKD (Table 5), development of proteinuria or microalbuminuria (Table 5), and hospitalization for causes related to CKD (Supplementary Tables S1 and S2). Four studies examined different outcomes, alone or in combination (1 examined hemodynamic pattern, 1 looked at mortality caused by CKD, and 1 investigated outcomes associated with kidney biopsy) (Supplementary Table S1).

Although ESRD and hospitalization were dichotomous in all articles, kidney function was analyzed in 7 articles as a dichotomous variable (CKD vs. normal kidney function or hyperfiltration vs. normal kidney function) and in 7 articles as continuous eGFR values by using different formulas (Modification of Diet in Renal Disease study equation, Chronic Kidney Disease Epidemiology Collaboration equation, and creatinine-cystatin equation; Table 5). Likewise, the presence of albuminuria was analyzed as a continuous covariate in 4 articles, according to a threshold in 7 articles and in both ways in 2 studies (Table 5). The modalities were however different and included 24-hour urine collections and/or albumin/creatinine ratio (Tables 3 and 5).

The studies selected reported on a consistent proportion of the exposed population; completeness of selection was higher in linkage databases and in studies based on questionnaires; completeness was consistently lower in cross-sectional analyses of populations selected on the basis of pregnancy data recorded 4 to 30 years previously, the range going from 20% to 100% (Supplementary Table S3A–C).

Quality of the studies, heterogeneity, and publication bias

The evidence was rated as of overall low quality by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale because of the observational nature of the studies; however, studies were rated as of fair to good quality in the National Institutes of Health scale, which is focused on observational studies (Supplementary Tables S4 and S5). This discrepancy is due to the fact that the GRADE scale is focused on the absolute value of the evidence whereas the National Institutes of Health scale considers the specific limitations of each study in the framework of their intrinsic limitations.

Indeed, even if the National Institutes of Health scale is considered, no study was fully unbiased, as was to be expected given the retrospective nature of the analyses. Clinical heterogeneity was high.

Statistical heterogeneity was also high: for the outcome ESRD, the study by Wang et al. accounted for most of heterogeneity, with I^2 decreasing from 94% to 23%.[53] For CKD,

the studies by Wang et al.[53] and Ayansina et al.[48] contributed to most of heterogeneity, with I^2 decreasing from 98% to 60%. The study by Paauw et al. contributed to most of heterogeneity of GFR, with I^2 decreasing from 83% to 73%.[43] For albuminuria, the study by McDonald et al. contributed to virtually all heterogeneity,[55] and for hospitalization, the study by Kessous et al. contributed to most of heterogeneity, with I^2 decreasing from 85% to 44%.[49]

The funnel plot analysis reveals a substantial symmetry for ESRD and eGFR, suggesting the absence of publication bias. For the outcomes CKD and hospitalization, a gap in bottom corners of the graphs suggest that small nonsignificant studies had been omitted in both directions, balancing the effect estimate. For albuminuria, a gap in the bottom left corner of the graph suggests that a protective effect of PE was omitted, leading to a possible mild overestimation of the effect of PE (funnel plots are shown in Supplementary Figures S1–S5).

Descriptive analysis: risk of ESRD

The definition of outcomes was homogeneous only for ESRD, whose incidence was recorded over time, leading to the construction of specific, albeit differently built curves: event-free in the articles from Taiwan[50,53] and incidence in the articles from Norway[54,58–60] (Table 4). It should be noted that the curves of patients with or without PE start differentiating from the fourth year of observation in Norway and from the beginning of the observation in Taiwan; in both cases the differences are statistically significant. None of the studies adjust for predialysis mortality, a potential attrition bias, because of the higher mortality in patients with CKD than in the overall population.

Descriptive analysis: risk of CKD and proteinuria

The development of CKD was analyzed in different ways—dichotomized at eGFR of 60 ml/min per 1.73 m^2 or eGFR as a continuous variable—by using different formulas (Modification of Diet in Renal Disease study equation and Chronic Kidney Disease Epidemiology Collaboration equation) and different tests, as reported in Table 3. No significant difference in eGFR was observed, but the difference (increase in CKD after PE) is significant in the dichotomous analysis in most single studies (Table 5).

A similar pattern is observed in the case of protein excretion, expressed as microalbuminuria, as well as protein/creatinine ratio (Table 5).

Correction for dialysis initiation was attempted in 1 article (no case recorded),[43] while none reported adjustment for mortality, possibly because of the rarity of this event in young women. The overall prevalence of CKD in the meta-analyzed control populations, excluding the 2 articles whose outcome was hyperfiltration, was low (1508 events per 234,068 controls [0.64%]).

Other outcomes include mortality, hospitalization, and need for kidney biopsy (Supplementary Tables S1 and S2; meta-analysis shown in Supplementary Figure S6).

Table 1 | Main characteristics of the studies included

Study	Country	Period of pregnancy	Period of study	Design	Exposed/not exposed	Aim of the study (as reported in the article)	Duration of follow-up after pregnancy (yr)	Renal outcome(s) (other outcomes)
Paauw et al.[43]	NL	1997–1998	1997–2012	Cohort study (PREVEND study); linkage with the ESRD registry	977/1805	To evaluate the incidence of CKD and ESRD and the course of kidney function after a *hypertensive disorder of pregnancy* in a longitudinal setting	11	CKD, ESRD, albuminuria
Lopes van Balen et al.[44]	NL	NA	Until 2011	Retrospective cohort, cross-sectional evaluation	79/49	To test the hypothesis that in women with a history of *PE*, kidney function correlates with endothelium-dependent flow-mediated vasodilation	4.4	CKD, microalbuminuria, (FMD)
Tooher et al.[45]	AU	1980–1989	NA	Retrospective record linkage	1158 (1364 pregnant)/27,262	To examine whether the *hypertensive disorders of pregnancy* affect women's future cardiovascular health	20 (3–29)	Hospitalization for CKD (separately: HT, CVD, stroke)
Bokslag et al.[46]	NL	1998–2005	2014–2016	Retrospective cohort, cross-sectional evaluation	131/56	To assess cardiovascular risk factors and established cardiovascular disease in women after *early-onset PE*, in the fifth decade of life	13.1 ± 2.2	CKD, microalbuminuria
Paauw et al.[47]	NL	1991–2007	2009–2010	Cohort study (PREVFEM study); cross-sectional evaluation	339/332	To study renal function in a large cohort of well-characterized women with previous *early-onset PE*, 10 yr postpartum	9.1 ± 3.7	CKD, proteinuria
Ayansina et al.[48]	GB-SCT	1950–2008	2009	Retrospective record linkage	811[a]/10,457	To assess the long-term effects of the *hypertensive disorders of pregnancy* on kidney function by using a population-based cohort, adjusting for confounders	>15	CKD, hospitalization for CKD
Kessous et al.[49]	IL	1988–2012	2012	Retrospective record linkage	7824/88,546	To investigate whether *severe and recurrent PE* increase the risk for long-term atherosclerotic morbidity (cardiovascular and renal)	11.2	CKD, hospitalization for CVD
Wu et al.[50]	TW	1998–2002	NC	Retrospective cohort (registry data)	13,633/930,841	To determine the long-term postpartum risk of ESRD in women with *hypertensive disorders in pregnancy*	9 (7.79–10.02)	ESRD
Sandvik et al.[51]	NO	1998–2000	2009–2010	Retrospective cohort, cross-sectional evaluation	89/69	To investigate the occurrence of the early stages of CKD after a single *PE pregnancy*	10.9 ± 1	CKD, microalbuminuria

Männistö et al.[52]	FI	1966	1967–2008[b]	Retrospective record linkage	242/6552	To evaluate the long-term risk in women for subsequent cardiovascular, cerebrovascular, and CKD as well as CVD mortality associated with the *full spectrum of hypertensive disorders during pregnancy*	39.4 (3.0–43.6)	CKD (CVD, cerebrovascular disease, diabetes, HT)
Wang et al.[53]	TW	1996–2009 or 1998–2009	2009	Retrospective record linkage	17,998[c]/213,397	To investigate the risk of ESRD among Taiwanese women who had a *hypertensive disorder* during pregnancy	6.3	CKD, ESRD
Vikse et al.[54]	NO	1967–2008	2009	Retrospective record linkage	First pregnancy: 25,821/544,854 Second pregnancy: 8977/27,7233	To assess the role of genetic and environmental contributions to the association between *PE* and ESRD, investigating the occurrence of ESRD in relatives of women with PE in their first pregnancy	19.6 ± 10.4	ESRD
McDonald et al.[55]	International	NA	2003–2005	Recall questionnaires, cross-sectional evaluation in RCT (ORIGIN trial)	467[d]/3613	To explore the relationship between *PE (severe and nonsevere)* and CVD after accounting for albuminuria and other known cardiovascular risk factors	NA[e]	CKD, microalbuminuria (CVD)
Bhattacharya et al.[56]	GB-SCT	Database started in 1950	2007	Retrospective record linkage	2026[f]/23,937	To examine the relationship between the *hypertensive disorders of pregnancy* and future hospital admittance for selected conditions, cancer, and death	>30	Mortality and hospitalization for CKD
Shahbazian et al.[57]	IR	2001–2003	NA	Retrospective cohort, cross- sectional evaluation	35/35	To assess whether women with a history of *PE* had higher rates of hypertension and microalbuminuria compared with women with uneventful pregnancy	5.7 (5.2–7.3)	CKD, microalbuminuria (HT)
Vikse et al.[58]	NO	1988–2005	2005	Retrospective record linkage	60/522	To investigate whether *PE and other adverse pregnancy outcomes* were associated with late renal damage and increased risk of progression of established CKD	Up to 16 after biopsy; age at first pregnancy, 24 ± 8.4; age at biopsy, 41.3 ± 4.8	ESRD
Sandvik et al.[59]	NO	1967–1994	2004 or 2005[b]	Retrospective record linkage	216/1265	To assess the extent to which *adverse pregnancy outcomes* were associated with later development of ESRD or premature death in women with diabetes	Up to 37	ESRD (death)

Table 1 | (Continued) Main characteristics of the studies included

Study	Country	Period of pregnancy	Period of study	Design	Exposed/not exposed	Aim of the study (as reported in the article)	Duration of follow-up after pregnancy (yr)	Renal outcome(s) (other outcomes)
Vikse et al.[60]	NO	1967–1991	2004	Retrospective record linkage	20,918/549,515	To assess the association between PE in ≥1 pregnancy and the development of ESRD	26.5 ± 7.5 after the first pregnancy	ESRD
Lampinen et al.[61]	FI	1996–1998	NA	Retrospective cohort, cross-sectional evaluation	30/21	To assess whether the degree of proteinuria in severe PE is related to impairment of vascular dilatation and/or kidney function years after pregnancy	5–6	CKD, microalbuminuria (FBF)
Vikse et al.[62]	NO	1967–1998	2002	Retrospective record linkage	29,317/72,7103	To assess whether perinatal outcomes are associated with later clinical CKD diagnosed by kidney biopsy	15.9 ± 9.4	Kidney biopsy
Shammas et al.[63]	JO	1988	10 yr later	Retrospective cohort, cross-sectional evaluation	47[9]/46	To assess the development of hypertension and its relation to renal function 10 yr after a pregnancy complicated by PE or PIH	10	CKD, microalbuminuria (HT)

AU, Australia; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; FBF, forearm blood flow; FI, Finland; FMD, flow-mediated dilatation; GB-SCT, Great Britain–Scotland; GH, gestational hypertension; HDP, hypertensive disorders of pregnancy; HT, hypertension; IL, Israel; IR, Iran; JO, Jordan; NA, not available; NC, not clear; NL, The Netherlands; NO, Norway; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PE, preeclampsia; PIH, pregnancy-induced hypertension; PREVEND, Prevention of Renal and Vascular End-stage Disease; PREVFEM, Preeclampsia Risk EValuation in FEMales; RCT, randomized controlled trial; TW, Taiwan.

In the table we kept all the studies using the same databases, if they did so for different periods or for different outcomes: 6 used the Medical Birth Registry of Norway[51,54,58–60,62], 2 used Taiwan's National Health Insurance Research Database,[50,53] and 2 used Aberdeen Maternity and Neonatal Databank[48,56]; only 1 database was further analyzed for each outcome.

[a]Ayansina et al.: Women with GH are not considered in our study (women with GH: 3583).
[b]Different databases.
[c]Wang et al.: Women with HDP other than PE are not considered in our study (women with HDP: 26,651).
[d]McDonald et al.: 108 severe preeclampsia and 359 nonsevere preeclampsia.
[e]McDonald et al.: Follow-up >20 yr on the basis of study design.
[f]Bhattacharya et al.: Women with GH are not considered in our study (women with GH: 8891).
[g]Shammas et al.: Women with GH are not considered in our study (women with GH: 54).

Table 2 | Main definitions of exposure in the articles reviewed as well as the source of definition of PE

Study	Exposure	PE definition or source of criteria	PE assessment/PE database
Paauw et al.[43]	PIH, PE	International Society for the Study of Hypertension in Pregnancy, 2014[a]	Patient report validated by linking data to the registry of obstetric departments from 2 hospitals of the Netherlands
Lopes van Balen et al.[44]	PE	National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy, 2000[b]	Hospital database Radboud University, Nijmegen, The Netherlands
Tooher et al.[45]	PIH, PE, chronic HT, s-PE	Society of Obstetric Medicine of Australia and New Zealand, 2008[c]	Hospital database Metropolitan tertiary hospital, Sydney, Australia
Bokslag et al.[46]	Early-onset PE	American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy, 2013[d] Severe PE: Presence of 1 or more of the following: proteinuria ≥5 g/24 h, HELLP syndrome, eclamptic seizure, pulmonary edema Early-onset PE: International Society for the Study of Hypertension in Pregnancy, 2001[e]	Hospital databases Two tertiary medical centers in the Netherlands
Paauw et al.[47]	Early-onset PE	Early-onset PE: International Society for the Study of Hypertension in Pregnancy[f]	Hospital database Isala Kliniieken, Zwolle, The Netherlands
Ayansina et al.[48]	PE, E, PIH	The classification and definition of the hypertensive disorders of pregnancy (Davey and MacGillivray[64]), 1988[g]	Aberdeen Maternity and Neonatal Databank
Kessous et al.[49]	PE	NA	Hospital database Perinatal Soroka University Medical Centre, Negev, Israel
Wu et al.[50]	PE, E, PIH, superimposed PE	Blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or both, and daily urine protein ≥0.3 g or ≥1+ on a urinary dipstick reading in a random urine sample that arises at the >20th wk of gestation	Taiwan's National Health Insurance Research Database
Sandvik et al.[51]	PE	National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy, 1990[h]	Medical Birth Registry of Norway
Männistö et al.[52]	PE, E, PIH, superimposed PE	Guidelines of the National Heart, Lung, and Blood Institute, 2000[i]	Northern Finland Birth Cohort
Wang et al.[53]	PE, E, PIH	Canadian Hypertension Society Consensus Conference, 1997[j]	Taiwan's National Health Insurance Research Database
Vikse et al.[54]	PE	American College of Obstetricians and Gynecologists, 1990[k]	Medical Birth Registry of Norway
McDonald et al.[55]	PE (severe and nonsevere)	National High Blood Pressure Education Program Working Group, 1990[l] Severe PE: Spectrum of organ dysfunction including seizures (eclampsia) Nonsevere PE: Hypertension and proteinuria developing in the last half of pregnancy	Patient report (questionnaire)
Bhattacharya et al.[56]	PE, E, PIH	Diastolic pressure >90 mm Hg on 2 occasions at least 4 h apart or a single reading of >110 mm Hg from the 20th wk of gestation onward in a previously normotensive woman plus at least 1 episode of proteinuria 0.3 g/24 h	Aberdeen Maternity and Neonatal Databank
Shahbazian et al.[57]	PE, E	Blood pressure ≥140/90 mm Hg and urinary protein excretion of ≥300 mg/24 h after the 20th wk of gestation	Hospital database Razi Hospital and Emam Khomeini Hospital, Ahvaz, Iran
Vikse et al.[58]	PE	American College of Obstetrics and Gynecologists, 1990[k]	Medical Birth Registry of Norway
Sandvik et al.[59]	PE	American College of Obstetrics and Gynecologists, 1990[k]	Medical Birth Registry of Norway
Vikse et al.[60]	PE	American College of Obstetrics and Gynecologists, 1990[k]	Medical Birth Registry of Norway

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Table 2 | (Continued) **Main definitions of exposure in the articles reviewed as well as the source of definition of PE**

Study	Exposure	PE definition or source of criteria	PE assessment/PE database
Lampinen et al.[61]	PE	NA	Hospital database Helsinki University Central, Helsinki, Finland
Vikse et al.[62]	PE	American College of Obstetrics and Gynecologists, 1990[k]	Medical Birth Registry of Norway
Shammas et al.[63]	PE	NA	Hospital database King Hussein Medical Center, Amman, Jordan

E, eclampsia; HELLP, hemolysis, elevated liver enzymes, low platelet; HT, hypertension; NA, not available; PE, preeclampsia; PIH, pregnancy-induced hypertension; s-PE, superimposed preeclampsia.

[a]New onset of hypertension (>140 mm Hg systolic or >90 mm Hg diastolic) after the 20th wk of gestation and the coexistence of 1 or more of the following new-onset conditions: proteinuria (spot urine protein/creatinine ratio >30 mg/mmol [0.3 mg/mg] or >300 mg/d or at least 1 g/L ["2+"] on dipstick testing); other maternal organ dysfunction (renal insufficiency [creatinine >90 μmol/l; 1.02 mg/dl]; liver involvement (elevated transaminases—at least twice the upper limit of normal with or without right upper quadrant or epigastric abdominal pain); neurological complications (examples include eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, and persistent visual scotomata); hematological complications (thrombocytopenia—platelet count <150,000/dl, diffuse intravascular coagulation, and hemolysis).

[b]Blood pressure >140 mm Hg systolic or >90 mm Hg diastolic in a woman who was normotensive before the 20th wk of gestation (gestational blood pressure elevation) accompanied by proteinuria. In the absence of proteinuria, the disease is likely to be present when increased blood pressure appears accompanied by any of the following symptoms: headache, blurred vision, and abdominal pain, or by abnormal laboratory test results, specifically low platelet counts and abnormal liver enzyme values.

[c]Increase in systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or both, after the 20th wk of gestation associated with the involvement of at least 1 other organ manifestation.

[d]Hypertension with 1 or more of the following new-onset conditions: proteinuria, thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbances.

[e]Delivery before the 34th wk of gestation, blood pressure >140/90 mm Hg, and proteinuria >300 mg/24 h.

[f]Diastolic blood pressure ≥90 mm Hg with proteinuria (≥0.3 g/24 h) diagnosed between the 20th and 32nd wk of gestation.

[g]Diastolic pressure >90 mm Hg on 2 occasions at least 4 h apart or a single reading of >110 mm Hg; from the 20th wk of gestation onward in a previously normotensive woman plus at least 1 episode of proteinuria of 0.3 g/24 h. Increased BP after the 20th wk of gestation (>140/90 mm Hg) and proteinuria (>0.3 g in a 24-h urine specimen or ≥1+ on a urinary dipstick reading).

[h]Women normotensive before the 20th gestational week but hypertensive (blood pressure ≥145 mm Hg systolic and ≥95 mm Hg diastolic) after the 20th gestational week with proteinuria in ≥1 sample.

[i]New-onset hypertension (blood pressure >140/90 mm Hg) with proteinuria of at least 300 mg in a 24-h urine sample after the 20th wk of gestation.

[j]Increased blood pressure after the 20th wk of gestation (blood pressure ≥140/90 mm Hg, or an increase in systolic blood pressure of ≥30 mm Hg or in diastolic blood pressure of ≥15 mm Hg, from measurements before the 20th wk of gestation) and proteinuria (≥0.3 g in a 24-h urine specimen or ≥1+ on a urinary dipstick reading).

[k]Pregnancy-induced hypertension with albuminuria, which arises after the 20th wk of gestation.

Meta-analysis: ESRD and albuminuria

The only outcome found to be significant in the meta-analysis is the risk of ESRD; as the databases are partially overlapping, we included only the largest cohorts (Vikse[54] and Wang[53]) (Figure 2). The risk of ESRD is significantly higher after PE (meta-analytic risk ratio [RR], 6.35; 95% confidence interval [CI], 2.73–14.79).

We are uncertain whether there is an increased risk of albuminuria after PE: statistical significance is not reached and CIs are wide, indicating lack of precision in the estimate (meta-analytic RR, 4.31; 95% CI, 0.95–19.58) (Figure 3); CKD was dichotomized at 60 ml/min per 1.73 m^2 (RR, 2.03; 95% CI, 0.58–7.32) (excluding 2 studies dealing with hyperfiltration) (Figure 4).

No difference is observed if eGFR is analyzed as a continuous variable (Supplementary Figure S7). The relative risk of hospitalization is also not significantly different (meta-analytic RR, 1.69; 95% CI, 0.98–2.92) (Supplementary Figure S6).

Stratification for duration of follow-up (dichotomized at 10 years) and region of origin (Europe vs. rest of the world) did not substantially modify results as for ESRD and CKD (Supplementary Figures S8 and S9). Conversely, the exclusion of 1 study (McDonald et al.[55]) in the stratification for follow-up, because of the lack of a precise follow-up measure, modifies the RR for albuminuria, whose risk reaches statistical significance (albuminuria: RR, 8.24; 95% CI, 3.07–22.10). Of note, the excluded study accounted for most of heterogeneity (Supplementary Figures S8A–C and 9A–C).

Number of cases that need to be followed up over time to identify an adverse long-term event. In the case of ESRD, the cumulative estimate of the number of cases needed to detect 1 adverse event (calculated as "number needed to treat" [NNT]) was 310 (95% CI, 120–959). The cumulative prevalence of ESRD was 0.06%, in keeping with a prevalence of ESRD of ∼0.1% in the overall population (this population consists of relatively young women with a lower incidence of ESRD).

The calculations of the NNT lead to 4 for albuminuria and 157 for CKD (CIs were not calculated because the meta-analytic RRs do not reach statistical significance). However, because the crude prevalence of CKD in the control population was only 0.64%, which is remarkably lower than the prevalence of CKD usually reported (estimated as ∼3% in women of childbearing age), we considered it likely that this figure is overestimated.

DISCUSSION

PE is a protean disease, which may exert long-term effects on cardiovascular and kidney health, whose entity is however not completely known. As a consequence, follow-up after a PE episode is not established.[1–4,13–23,31–41]

There are several reasons why the results of the analyses of these long-term health effects are not fully clear: the pathogenesis of PE is only partially understood; the recent trend

Table 3 | Main definition and assessment of biochemical data included in outcomes in studies reporting on kidney function or proteinuria

Study	Renal outcome(s)	CKD–eGFR	C/D	Microalbuminuria	C/D
Paauw et al.[43]	CKD, microalbuminuria	*Crs:* Enzymatic method *CysC:* Turbidimetric assay *eGFR:* CKD-EPI equation, creatinine-cystatin equation *Threshold:* eGFR <60 ml/min per 1.73 m²	D	*Method:* Nephelometry (UAE in 24-h urine collection) *Threshold:* >30 mg/d	D
Lopes van Balen et al.[44]	CKD, microalbuminuria	*Crs:* Colorimetric enzymatic method *eGFR:* CKD-EPI equation *Threshold:* None	C	*Method:* Immunonephelometry (ACR in 24-h urine collection) *Threshold:* None	C
Bokslag et al.[46]	CKD, microalbuminuria	*Crs:* NA *eGFR:* NA *Threshold:* None	C	*Method:* NA (ACR in a morning urine sample) *Threshold:* None	C
Paauw et al.[47]	CKD, proteinuria	*Crs:* Colorimetric enzymatic method *eGFR:* CKD-EPI equation and MDRD study equation *Threshold:* eGFR <60 ml/min per 1.73 m²	C, D	*Method:* Turbidimetric method (protein/creatinine ratio) *Threshold:* >30 mg/mmol	D
Ayansina et al.[48]	CKD	*Crs:* Colorimetric method *eGFR:* MDRD study equation *Threshold:* eGFR <60 ml/min per 1.73 m² (≥90 d)	D	NA	
Männistö et al.[52]	CKD	*Crs:* NA *eGFR:* NA *Threshold:* NA (probably eGFR of 60 ml/min per 1.73 m²)	D	NA	
Wang et al.[53]	CKD	*Crs:* NA *eGFR:* NA *Threshold:* NA (probably eGFR of 60 ml/min per 1.73 m²)	D	NA	
McDonald et al.[55]	CKD, microalbuminuria	*Crs:* Colorimetric method *eGFR:* MDRD study equation *Threshold:* NA (probably eGFR of 60 ml/min per 1.73 m²)	C, D	*Method:* Turbidimetric method (ACR in a morning urine sample) *Threshold:* Microalbuminuria if range between 3.4 and 34.9 mg/mmol	C, D
Shahbazian et al.[57]	CKD, microalbuminuria	*Method:* NA *mGFR:* Creatinine clearance *Threshold:* None	C	*Method:* NA (ACR in a morning midstream urine sample) *Threshold:* ≥30 mg/mmol	D
Lampinen et al.[61]	CKD, microalbuminuria	*Crs:* Colorimetric enzymatic method *eGFR:* NA *Threshold:* None	C	*Method:* Immunoturbidimetric method (UAE in 24-h urine collection) *Threshold:* >30 mg/24 h	C, D
Shammas et al.[63]	CKD, microalbuminuria	*Crs:* NA *eGFR:* NA *Threshold:* None	C	*Method:* NA (UAE in 24-h urine collection) *Threshold:* Excretion of 20–200 mg/24 h	D
Sandvik et al.[51]	CKD, microalbuminuria	*Crs:* Enzymatic method *eGFR:* CKD-EPI equation *Threshold for high-normal eGFR:* >114.3 ml/min per 1.73 m²	D	*Method:* Nephelometry (ACR in 3 morning urine samples) *Threshold:* >2.5 mg/mmol	D

ACR, albumin/creatinine ratio; C, continuous; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Crs, serum creatinine; CysC, cystatin C; D, dichotomous; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NA, not available; UAE, urinary albumin excretion.

toward stratification of PE into different categories underlines the heterogeneity of the disease. These include maternal versus placental, severe versus mild, and related versus unrelated derangement of the angiogenic/anti-angiogenic balance.[17–22,65,66] Furthermore, the relationship between PE and the other hypertensive disorders of pregnancy is complex and one disease may merge with another.[65–68] Because of changes in definitions and heterogeneity across studies, subtle differences cannot be captured in retrospective analyses (Table 2).

The relationship between CKD and PE is likewise complex and non-univocal: on the one hand, PE may be a cause or a marker of future CKD; on the other hand, there is an increased occurrence of PE in patients with CKD and many predisposing factors, including diabetes, obesity, metabolic syndrome, and hypertension, are shared by PE and CKD.[34–42,69]

Available evidence allows us to conclude that there is an increased risk of kidney diseases after PE, but does not permit us to quantify that risk, something which must be done if follow-up strategies are to be defined. What distinguishes our review from the meta-analysis carried out by McDonald et al. is not only the inclusion of recent studies but also the focus on studies that include only medium- to long-term follow-up

Table 4 | Outcome: risk of ESRD, as reported in the articles reviewed

Study	Population	Cumulative incidence	Main results as reported in the articles
Paauw et al.[43]	Women aged 28–75 yr with microalbuminuria who had hypertension in pregnancy	No case	None developed ESRD during follow-up
Wu et al.[50]	Women in Taiwan's National Health Insurance Research Database who had deliveries between 1998 and 2000	Exposed: 46/13,633 Not exposed: 212/930,841	HR, 15.23; 95% CI, 11.07–20.95; $P < 0.001$
Wang et al.[53]	Women in the database of Taiwan's health care reimbursement claims in the 1996–2009 period with hypertensive disorders in first pregnancy who were 19–40 yr of age between 1998 and 2009	Exposed: 61/17,998 Not exposed: 45/213,397	HR, 15.9; 95% CI, 10.8–23.3 ; $P < 0.001$[a]
Vikse et al.[54]	All women registered in the Medical Birth Registry of Norway with a first birth in 1967–2008 period	First pregnancy: Exposed: 52/25,821[b] Not exposed: 222/503,583 Second pregnancy: Without children with PE Exposed: 39/8977[b] Not exposed: 340/277,233	First pregnancy: Without siblings with PE: RR, 5.95; 95% CI, 4.37–8.11 With siblings with PE: RR, 2.76; 95% CI, 0.88–8.63 Second pregnancy: Without children with PE: RR, 3.81; 95% CI, 2.67–5.43 With children with PE: RR, 2.97; 95% CI, 1.11–7.98
Vikse et al.[58]	All women registered in the Norwegian Kidney Biopsy Registry and Medical Birth Registry of Norway who, after their last recorded birth, had a representative kidney biopsy in 1988–2005	Exposed: 10/60 Not exposed: NR	First pregnancy: RR, 1.2; 95% CI, 0.63–2.4; $P = 0.5$ First or second pregnancy: RR, 1.4; 95% CI, 0.77–2.5; $P = 0.3$
Sandvik et al.[59]	Women registered in the Medical Birth Registry of Norway with a first singleton delivery between 1967 and 1994 with or without preeclampsia and diabetes diagnosed before pregnancy	Exposed: 11/216 Not exposed: 37/1265	Term birth: RR, 1.3; 95% CI, 0.41–4.4 Preterm birth: RR, 2.8; 95% CI, 1.3–6.0
Vikse et al.[60]	Women registered in the Medical Birth Registry of Norway with a first singleton delivery between 1967 and 1991 with or without PE	Exposed: 67/20,918 Not exposed: 410/549,515	After the first pregnancy: RR, 4.7; 95% CI, 3.6–6.1[c]

CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; NR, not reported; PE, preeclampsia; RR, risk ratio.
[a]Cox proportional hazards method.
[b]Vikse et al.: Cumulative incidence of ESRD in exposed and nonexposed women. Incidence of ESRD according to familial factors: exposed women without siblings with PE, 49/22,814; exposed women with siblings with PE, 3/3007; exposed women without children with PE, 35/7876; exposed women with children with PE, 4/1101.
[c]After the second pregnancy (women with ≥3 pregnancies): PE in first pregnancy only, RR, 3.2 (95% CI, 2.2–4.9); PE in second pregnancy only, RR, 6.7 (95% CI, 4.3–10.6); PE in both pregnancies, RR, 6.4 (95% CI, 3.0–13.5). After third pregnancy (women with ≥3 pregnancies): PE in first pregnancy only, RR, 14.4 (95% CI, 9.4–20.5); PE in second pregnancy only, RR, 7.3 (95% CI, 3.0–18.1); PE in third pregnancy only, RR, 14.3 (95% CI, 8.2–24.7); PE in ≥2 pregnancies, RR, 15.5 (95% CI, 7.8–30.8).

(at least 4 years, instead of at least 6 weeks postpartum).[42] The clinical and statistical heterogeneity of the studies examined is high, even with our narrower selection criteria; as a consequence, it was not possible to stratify data as for presence and type of maternal disease or characteristics of PE, and this led us to undertake the meta-analysis with a less robust random effects model.[43–63]

The point of follow-up is crucial: taking the renal functional reserve into account, if PE represents a substantial hit, but one affecting <50% of the kidney parenchyma, it is conceivable that CKD will only become clinically detectable after a long interval. In line with this observation, some articles suggested that the risk of ESRD was graduated according to the entity of the "PE hit" and reported it as higher in women who had >1 PE episode or who had PE versus gestational hypertension.[53,60] The lack of homogeneous definitions, however, does not allow stratifications as for number of episodes or severity of PE, suggesting to address this important issue in future research.

Probably because of the high heterogeneity of the available evidence, our study leads to an intriguing result: we found a significant association between PE and ESRD (meta-analytic RR, 6.35; 95% CI, 2.73–14.79), the most robust but rare outcome (Figures 2 and 3). We are uncertain whether there is an increased risk of albuminuria after PE: statistical significance is not reached and CIs are wide, indicating lack of precision in the estimate (meta-analytic RR, 4.31; 95% CI, 0.95–19.58). Furthermore, we failed to identify a significant relationship with the intermediate phase of kidney disease, that is, CKD (meta-analytic RR, 2.03; 95% CI, 0.56–7.32) (Figure 3). The reason why only the first (albuminuria) and last (ESRD) phases of CKD are weakly or strongly correlated to previous PE presumably resides in the limitations of the studies. In fact, the definition of ESRD is univocal; furthermore, ESRD registries are usually complete, and although none of the studies were able to control predialysis excess mortality, this is probably more relevant in elderly patients than in a

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clinical investigation

Table 5 | Outcome: risk of CKD and albuminuria, as reported in the articles reviewed

Study	Population	CKD results: eGFR (ml/min per 1.73 m^2)	Analysis	Albuminuria results	Analysis
Paauw et al.[43]	Women aged 28–75 yr with microalbuminuria who answered on hypertension in pregnancy	Exposed: 88.0 ± 16.1 Not exposed: 91.0 ± 15.3 HR, 1.04; 95% CI, 0.79–1.37; P = 0.8	C	Exposed: 9.0 mg/d (6.2–14.2 mg/d) Not exposed: 8.1 mg/d (6.0–13.7 mg/d) P = NA[a]	C
Lopes van Balen et al.[44]	Women at a single medical center in the Netherlands	Exposed: 105 ± 16 Not exposed: 98 ± 14 P = 0.55	C	Exposed: 0.5 g/mmol (0.4–1.1 g/mmol) Not exposed: 0.6 g/mmol (0.3–1.3 g/mmol) P = 0.92	C
		Exposed: 0/79 Not exposed: 0/49[b]	D	Exposed: 6/79 Not exposed: 0/49[b]	D
Bokslag et al.[46]	Women giving birth during 1998–2005 from obstetrical databases of 2 tertiary centers	Exposed: 90 (82–90) Not exposed: 90 (82–90) P = 0.805	C	Exposed: 4.4 g/mol (30–7.8 g/mol) Not exposed: 3.0 g/mol (3.0–3.9 g/mol) P = 0.015	C
Shahbazian et al.[57]	Primiparous women between 2001 and 2003	Exposed: 108 ± 14 Not exposed: 110 ± 17 P = 0.59	C	Exposed: 7/35 Not exposed: 0/35 P < 0.01 (data from the table)	D
Lampinen et al.[61]	Women who delivered during 1996–1998 with 24-h proteinuria	dU-prot <5 g: Exposed: 108 (70–126) dU-prot ≥5 g: Exposed: 126 (120–132) Not exposed: 126 (120–150)[c]	C	dU-prot <5 g Exposed: 5.5 mg/d (4–10 mg/d) dU-prot ≥5 g: Exposed: 7 mg/d (6–13 mg/d) Not exposed: 6 mg/d (4.5–9 mg/d)[c]	C
McDonald et al.[55]	Women aged ≥50 yr with dysglycemia who had a prior CVD event with at least 1 delivery and information about PE (ORIGIN trial)	Nonsevere PE: Exposed: Continuous: 74.8 ± 22.2 Dichotomous: 82/359 Severe PE: Exposed: Continuous: 74.1 ± 21.4 Dichotomous: 24/108 Not exposed: Continuous: 74.7 ± 22.2 Dichotomous: 940/3613[d]	C, D	Nonsevere PE: Exposed: Continuous: 5.8 ± 26.5 mg/mmol Dichotomous: 35/359 Severe PE: Exposed: Continuous: 5.6 ± 17.5 mg/mmol Dichotomous: 14/108 Not exposed: Continuous: 74.7 ± 22.2 mg/mmol Dichotomous: 940/3613[d]	C, D
Shammas et al.[63]	Women who delivered at King Hussein Medical Center in 1988 with PE or normal pregnancy	Exposed: 76 mmol/l[e] Not exposed: 77 mmol/l[e] P = NA	C	Exposed: 23/47 Not exposed: 3/46 P < 0.0001 (calculated)	D
Ayansina et al.[48]	Primiparous women born on or before June 30, 1969, with a singleton first delivery before June 30, 2008, beyond 20 wk of gestation identified from AMND	Exposed: 61/811 Not exposed: 405/10,457 OR, 2.02; (95% CI, 1.53–2.67; P < 0.001 HR, 1.70 ; 95% CI, 1.30–2.23; P < 0.001	D		
Männistö et al.[52]	Women of the Northern Finland Birth Cohort 1966 Deliver at >28 gestational weeks, birth weight of ≥600 g	Exposed: 2/242 Not exposed: 73/6552 HR, 0.75; 95% CI, 0.17–3.38; P > 0.05	D		
Wang et al.[53]	Women in the database of Taiwan's health care reimbursement claims in the 1996–2009 period who were 19–40 yr between 1998 and 2009	Exposed: 121/26,651 Not exposed: 90/213,397 HR, 10.8; 95% CI, 8.20–14.2	D		

Table 5 | (Continued) Outcome: risk of CKD and albuminuria, as reported in the articles reviewed

Study	Population	CKD results: eGFR (ml/min per 1.73 m^2)	Analysis	Albuminuria results	Analysis
Paauw et al.[47]	Women who delivered during 1991–2007 (PREVFEM study)	*MDRD study equation:* Exposed: 95 (86–105) Not exposed: 96 (85–110) $P = 0.33$ *CKD-EPI equation:* Exposed: 106 (93–113) Not exposed: 105 (94–111) $P = 0.40$	C, D^f	Continuous: Exposed: 8.5 mg/mmol (6.3–13.0 mg/mmol)[g] Not exposed: 7.1 mg/mmol (5.5–10.5 mg/mmol)[g] $P < 0.01$ Dichotomous: Exposed: 3.68% (12 cases) Not exposed: 3.70% (12 cases) $P > 0.05$	C, D
Sandvik et al.[51]	Living women registered in the Medical Birth Registry of Norway, 1998–2000 (first pregnancy)	Exposed: 27/89 Not exposed: 12/69 OR, 2.07; 95% CI, 0.96–4.46; $P = 0.06$	D^h	Exposed: 23/89 Not exposed: 17/69 OR, 1.06; 95% CI, 0.51–2.19; $P = 0.87$	D^f

AMND, Aberdeen Maternity and Neonatal Databank; ANOVA, analysis of variance; C, continuous; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; D, dichotomous; dU-prot, proteins in 24-h urine collection; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; NA, not available; OR, odds ratio; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PE, preeclampsia; PREVFEM, Preeclampsia Risk EValuation in FEMales.
[a]Paauw et al.: As reported in the article, no significant differences in 24-h albuminuria at all visits.
[b]Lopes van Balen et al.: Author's communication.
[c]Lampinen et al.: eGFR: $P = 0.08$ (overall ANOVA); albuminuria: $P = 0.3$ (overall ANOVA).
[d]McDonald et al.: Continuous eGFR: $P = 0.9553$; dichotomous eGFR: $P = 0.3002$; continuous albuminuria: $P = 0.7396$; dichotomous albuminuria: $P = 0.2954$.
[e]Shammas et al.: Creatinine values.
[f]Paw et al.: Analysis considers the outcome of hyperfiltration (eGFR >110 ml/min per 1.73 m^2); MDRD study equation: OR, 1.59 (95% CI, 1.09–2.33; $P = 0.02$); CKD-EPI equation: OR, 1.34 (95% CI, 0.97–1.86; $P = 0.08$).
[g]Paauw et al.: Protein/creatinine ratio values.
[h]Sandvik et al.: Analysis considers the outcome of hyperfiltration eGFR >75th percentile (114 ml/min per 1.73 m^2) and ACR >75th percentile (0.70 mg/mmol).

young female population. Albuminuria is more consistently defined in a dichotomous way, and its appearance usually precedes a reduction in kidney function: follow-up may be too short to evidence this decrease, but long enough to make it possible to discover albuminuria. Within the limitations of the studies, the meta-analysis allowed us to establish the number of patients who need to be followed up to detect an adverse long-term event for each outcome (NNT); the number of women who need to be followed up to detect 1 patient with ESRD is high (310; 95% CI, 120–959). Conversely, if we consider the NNT of 4 in the case of albuminuria, the benefit of organizing regular follow-up is more evident, given the importance of albuminuria as a global marker of cardiovascular health. In both cases, the wide CIs underline that the estimate lacks precision and needs to be refined through further studies. The NNT for ESRD is in line with the figures resulting from screening studies, which are often in the 500 to 2000 range to prevent 1 death over 5 years.[70–72] However, at difference with these studies in which the detection of a disease (e.g., colon or breast cancer) is rapidly followed by a medical choice, which usually leads to a medical treatment, in the case of ESRD, the detection occurs over a longer period of time, and ESRD represents the final phase of the disease. The lower NNT identified for albuminuria suggests that there may be a space for maneuver for prevention and early treatment, but the current knowledge does not allow further sound inference on the expected benefits (prevention of ESRD).

The interest in this review resides in the updated analysis of the rapidly accumulating evidence on the role of PE in the development of kidney disease and in the pragmatic evaluation of the organization of further follow-up.

This review has limitations, both because of the methodology chosen and because of the limitations of the literature we were able to retrieve. The review was undertaken with a rapid review of methodology, analyzing the 3 classical databases only—PubMed-MEDLINE, Embase, and Cochrane Library—and focusing on studies with a minimum number of 30 PE cases and a follow-up of at least 4 years, reported in articles published in the new millennium; the hand search was limited to references of review studies, and no search for unpublished data was performed.[73–80] These choices were made to limit heterogeneity, which we expected and found to be high, and to focus on studies that were likely to be informative for establishing follow-up policies. Conversely, all steps were performed in duplicate and analysis was undertaken in conformity with the Cochrane Collaboration methodology, choosing a random effects model to avoid enhancing the effects observed.[81]

Concerning the limitations of the literature, none of the studies we retrieved was prospective and populations and follow-up were diverse. Further limitations are intrinsic to the study designs: the best population coverage is attained in database linkage studies, whose limitations are those of the original databases; no correction for predialysis mortality was
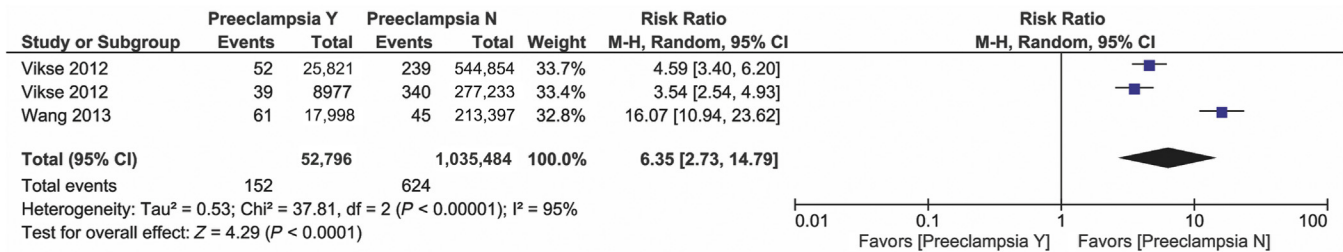
Figure 2 | Forest plot for the outcome end-stage renal disease. CI, confidence interval.

undertaken. The studies of incidence and prevalence of proteinuria and kidney function reduction are more heterogeneous, and the recruitment of the cases for the cross-sectional study is incomplete. Furthermore, evidence comes mainly from Europe (14 of 21 articles) and, although different parts of the world are represented, none of the studies retrieved comes from a low-income country, where the incidence of CKD is significantly higher and where PE is probably more frequent and more dangerous.

A further limitation, on which we suggest focusing future research, is the lack of uniform information and definition of maternal diseases and of the severity and timing of PE. The heterogeneity of the study designs and outcomes chosen reduced the possibility of performing meta-analyses, and the differences in outcomes are largely unexplained (even after stratification by follow-up times).

These limitations show the need for undertaking prospective cohort studies, which probably represent the only way to define kidney-related risks and to distinguish between the effects of the different facets of PE: revealer of the underlying kidney disease or a hit in the context of a multiple-hit pathogenesis. In this regard, follow-up after PE could be a powerful measure to prevent cardiovascular and kidney disease in the long-term.

METHODS

We followed the Meta-analysis Of Observational Studies in Epidemiology consensus statement for reporting meta-analysis of observational studies (Supplementary Item S1).[82]

We chose the methodology of a rapid review (more focused, essentially exploring the published articles, and limited to 3 main databases with arbitrary but clinically sound limits for the period of the study [2000–2018], number of cases of PE [at least 30], and length of follow-up [at least 4 years]).[73–80] We empirically chose the cut point of at least 4 years, considering that this could allow

detection of CKD (defined as GFR <60 ml/min per 1.73 m^2) in the presence of rapid progression of CKD, defined as loss of ≥ 10 ml/min per 1.73 m^2 of GFR per year (from normal GFR, defined as ≥ 90 ml/min per 1.73 m^2); furthermore, we considered that the onset of albuminuria was probably antedating the onset of kidney function impairment, and we wanted to leave broad criteria to capture events occurring in the early CKD phases.

No selection for the presence of baseline diseases was made.

Our aim was to obtain timely pragmatic responses to the question of whether the evidence of a negative effect of PE on kidney health is strong enough to lead us to change our clinical practice by organizing structured follow-up programs after a PE episode.

All steps of data selection and extraction were performed in duplicate by a team of 2 nephrologists (GBP and BC), one with a master's degree in systematic reviews. Database search, data selection, and data extraction quality assessment were performed in duplicate by following the classical indications of the *Cochrane Handbook* versions 5.1 and 5.3.[83,84] Quality assessment is described in that specific paragraph. Controversies were solved through discussion (EV and GC).

The review was prospectively registered in the PROSPERO database (registration no.: CRD42016043386, dated July 22, 2016).

Eligibility criteria and PICOS criteria

The eligibility criteria and PICOS criteria are as follows:

P (patients): women who had ≥ 1 episodes of PE during ≥ 1 pregnancy

I (intervention – exposure): exposure to PE

C (controls): women who had at least 1 uncomplicated pregnancy in the same setting and period of time

O (outcomes): long-term (at least 4 years of follow-up) development of CKD (reduction of kidney function and proteinuria), renal-related hospitalization, ESRD, or other relevant kidney health–related outcomes

S (studies): observational studies with a control population available, displaying at least 30 cases of PE, with a mean follow-up of at least 4 years, published between 2000 and 2018. No selection for language or quality was performed (see below).
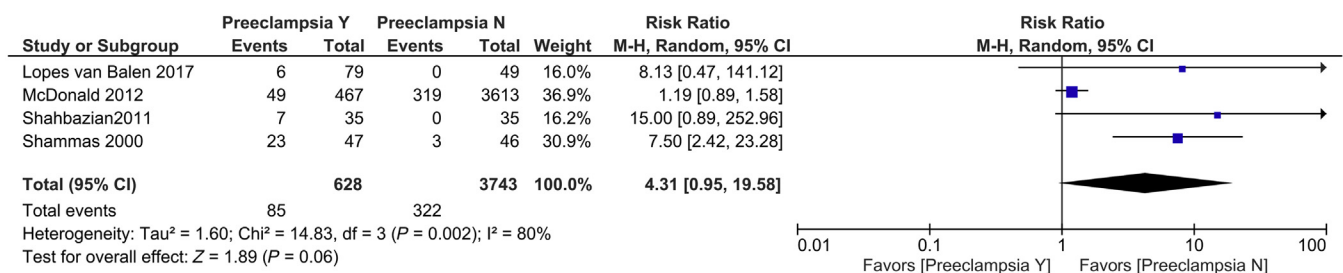

Figure 3 | Forest plot for the outcome albuminuria. CI, confidence interval.

Study or Subgroup	Preeclampsia Y Events	Total	Preeclampsia N Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ayansina 2016	61	811	405	10,457	26.5%	1.94 [1.50, 2.52]
Lopes van Balen 2017	0	79	0	49		Not estimable
Mannisto 2013	2	242	73	6552	20.3%	0.74 [0.18, 3.00]
McDonald 2012	106	467	940	3613	26.7%	0.87 [0.73, 1.04]
Wang 2013	121	26,651	90	213,397	26.5%	10.77 [8.20, 14.14]
Total (95% CI)		28,250		234,068	100.0%	2.03 [0.56, 7.32]
Total events	290		1508			

Heterogeneity: Tau² = 1.60; Chi² = 232.88, df = 3 ($P < 0.00001$); I² = 99%
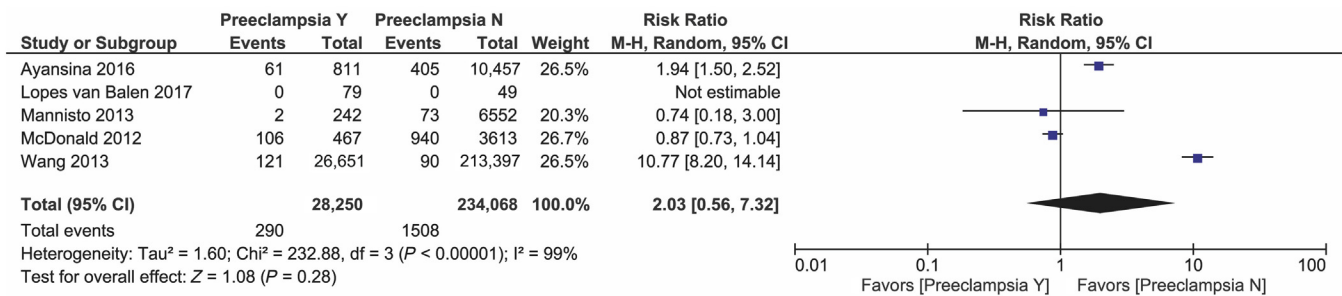Test for overall effect: $Z = 1.08$ ($P = 0.28$)

Figure 4 | Forest plot for the outcome chronic kidney disease (dichotomized at estimated glomerular filtration rate of 60 ml/min per 1.73 m²). CI, confidence interval.

Search strategy for the identification of studies

The following databases were searched in duplicate by GBP and BC: MEDLINE, Embase, and Cochrane databases of systematic reviews.

The following terms were used: preeclampsia OR gestosis OR eclampsia OR "hypertensive disorder of pregnancy" OR "hypertensive disorders of pregnancy" OR "pregnancy induced hypertension" OR "pregnancy induced hypertensive disorder" OR "pregnancy induced hypertensive disorders" OR PIH OR HELLP; they were combined with CKD OR "chronic kidney disease" OR dialysis OR hemodialysis OR ESRD OR "end stage kidney disease" OR "end stage renal disease" OR proteinuria OR renal outcome OR renal disease OR kidney disease OR albuminuria OR microalbuminuria.

The period of the search was January 1, 2000, to May 31, 2018.

No language limitation was applied, as the authors as a group understand several European languages, and if needed, they can obtain help for other languages (this did not occur in this review). We reviewed in duplicate reference lists of all studies retrieved in full text; in keeping with rapid review methods, we limited the search of abstracts to those published in the selected databases; in cases where missing or incomplete data would have interfered with meta-analysis, all authors were contacted by BC via e-mail (twice in the case of no response).

Duplicate publications

In the case of duplicate or partially duplicate publications (i.e., in the same databases in the case of linkage analysis), we followed the following criteria: for duplicate series, all articles have been included if they deal with different outcomes; in the case of >1 article from the same source and on the same outcome, only 1 is included in each meta-analysis; in these cases, either the full article (in the case of abstract and full article) or the most recent article has been chosen.

For partially duplicate publications (same databases, overlapping but nonidentical selections), the largest cohort and, in the case of similar numbers, the most recent one was selected for meta-analysis; all are included in the descriptive analysis and different outcomes are analyzed as previously described.

Data collection and analysis

We extracted the following information from each study (BC and GBP): population (characteristics of the population, including age, parity, ethnicity, presence or absence of predisposing diseases, such as diabetes or hypertension; inclusion or exclusion of twin pregnancies; and all other relevant information as reported in the articles); number of cases and number of controls; type of study design; aims (as reported in the article); country(ies) where study was performed; period of pregnancy; period of study; follow-up after pregnancy (as reported in the article); type of exposure (PE, hypertensive disorders of pregnancy, and their definitions, whenever available); type of outcomes (definition of all outcomes, including laboratory assessment, if available); type of data analysis; and health outcomes (however defined in the articles; the definitions were also extracted): ESRD, CKD, albuminuria, proteinuria, hospitalization for kidney-related causes, and other relevant outcomes related to CKD (as reported in the articles).

Quality assessment

Quality of the evidence was assessed by EV and GBP according to the GRADE scale[85]; however, because observational studies are uniformly rated as of low quality by the GRADE scale, the single studies were also was scored by BC and EV according to the National Institutes of Health criteria.[86] This latter choice was based on simplicity, reproducibility, and the possibility of giving an overall, individually weighted quality score for each qualitative characteristic of the studies.

Selection on the basis of quality of the study was not performed; however, all the studies are of fair or good quality according to the National Institutes of Health criteria.

Assessment of reporting biases and of heterogeneity

We assessed publication bias through the funnel plot method for each outcome measure.[87] Significance was tested as recommended by Higgins and Green.[83]

We performed a test of heterogeneity when ≥2 studies were included in the meta-analysis. We assessed statistically significant heterogeneity between primary outcome studies using the chi-square test and I² statistic. We considered a significant χ^2 ($P < 0.01$) and an I² value of at least 50% as statistical heterogeneity. We identified studies that most heavily influenced heterogeneity and performed a sensitivity analysis by omitting them.

Subgroup analyses

We planned to perform subgroup analyses using the following factors: duration of follow-up, considering the hypothesis that only the longest follow-up would make it possible to detect robust outcomes, such as ESRD; severity, timing of PE, and presence of baseline maternal diseases (superimposed, severe, and early PE could be associated with worse health outcomes); age at pregnancy (older women have a higher risk of both PE and CKD or ESRD); and setting for the analysis. However, either the number of studies making these analyses was too low or data were reported in a highly heterogeneous way, not allowing any sound stratification (as in the case of severity, timing of PE, and presence of maternal diseases).

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Within these limitations, we attempted stratification as for setting of care (Europe vs. other countries) and duration of follow-up (dichotomized at 10 years), acknowledging the clinical importance of these issues.

Data synthesis

When possible, we combined the outcome measures from the individual studies through meta-analysis; we planned to use a fixed effects model in the case of low heterogeneity and a random effects model in the case of high heterogeneity.

The random effects method incorporates the assumption that different studies estimate different yet related intervention effects.[88] The method is based on the inverse variance approach, making an adjustment to the study weights according to the extent of variation, or heterogeneity, between the varying intervention effects.

For meta-analysis we used Review Manager (RevMan 5.3).[84] The forest plot was used to synthesize results. Studies partially or completely answering our PICOS criteria were included in the analysis by using homogeneous measures of effect.

Sensitivity analyses were performed using different effect size measures (e.g., odds ratios and standardized mean differences).

Measures of health effect

For dichotomous outcomes we calculated RRs and 95% CIs.

For continuous outcomes we calculated mean difference between groups and 95% CIs to summarize results across studies.

On the basis of meta-analytic RRs, we estimated the frequency of an event in the PE group and consequently the number of patients with PE who need follow-up to identify an adverse health outcome (corresponding to NNT) and 95% CIs by using the formulas for NNT.[89]

We performed scenario analysis, testing 2 hypotheses of CKD, one based on the dichotomous data analyzed in the meta-analysis and the other based on the hypothesis that the relationship between cases of ESRD and cases of CKD stages 3–5 not on dialysis was the same as reported in the overall population, with a rounded prevalence of ESRD of 0.1% versus 5% in patients with CKD stages 3–5 not on dialysis.[69] In the case of nonsignificant results, 95% CIs were omitted in accordance with Altman.[89]

DISCLOSURE
All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL
Figure S1. Funnel plot of comparison: exposed versus not exposed to preeclampsia for the outcome CKD (eGFR < 60 ml/min per 1.73 m^2).
Figure S2. Funnel plot of comparison: exposed versus not exposed to PE for the outcome CKD (continuous eGFR).
Figure S3. Funnel plot of comparison: exposed versus not exposed to PE for the outcome ESRD.
Figure S4. Funnel plot of comparison: exposed versus not exposed to PE for the outcome albuminuria (dichotomous).
Figure S5. Funnel plot of comparison: exposed versus not exposed to PE for the outcome hospitalization.
Figure S6. Forest plot: exposed versus not exposed to PE for the outcome hospitalization.
Figure S7. Forest plot: exposed vs not exposed to PE for the outcome e-GFR (continuous eGFR).

Figure S8. (**A**) Forest plot: exposed vs not exposed to PE stratified for duration of follow-up: ESRD. (**B**) Forest plot: exposed vs not exposed to PE stratified for duration of follow-up: albuminuria. (**C**) Forest plot: exposed vs not exposed to PE stratified for duration of follow-up: CKD (eGFR <60 ml/min per 1.73 m^2).
Figure S9. (**A**) Forest plot: exposed vs not exposed to PE stratified for setting of follow-up: ESRD. (**B**) Forest plot: exposed vs not exposed to PE stratified for setting of follow-up: albuminuria. (**C**)Forest plot: exposed vs not exposed to PE stratified for setting of follow-up: CKD (eGFR <60 ml/min per 1.73 m^2).
Table S1. Other outcomes, including hospitalization, as reported in the articles.
Table S2. Hospitalization codes considered for analysis.
Table S3A. Inclusion, exclusion criteria, and ratio between "at-risk" and examined cases.
Table S3B. Inclusion, exclusion criteria, and selected cases: retrospective and cross-sectional studies.
Table S3C. Inclusion, exclusion criteria, and selected cases: other study designs.
Table S4. Summary table and quality assessment according to the GRADE evaluation tool.
Table S5. Quality assessment according to the National Institutes of Health evaluation tool.
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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