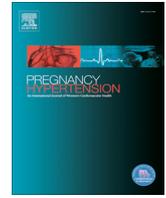




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# Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

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## Long term effects of gestational hypertension and pre-eclampsia on kidney function: Record linkage study

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### ABSTRACT

**Objective:** To assess the long term effects of hypertensive disorders of pregnancy on renal function.

**Design:** Cohort study where exposure was gestational hypertension or preeclampsia in the first pregnancy. Normotensive women formed the comparison group.

**Setting:** Aberdeen, Scotland.

**Participants:** All women with date of birth on or before 30th June 1969 and at least their first singleton delivery recorded in the Aberdeen Maternity and Neonatal Databank.

**Methods:** Participants were linked to the Renal Biochemistry Register, Scottish Morbidity Records, Scottish Renal Registry and National Register for deaths.

**Main outcome measures:** Occurrence of chronic kidney disease (CKD) as identified from renal function tests in later life, hospital admissions or death from kidney disease or recorded as receiving renal replacement therapy.

**Results:** CKD was diagnosed in 7.5% and 5.2% of women who previously had GH and PE respectively compared to 3.9% in normotensive women. The unadjusted odds ratio (95% confidence interval) of having CKD in PE was 2.04 (1.53, 2.71) and that for GH was 1.37 (1.15, 1.65), while the adjusted odds ratio (95% confidence interval) of CKD was 1.93 (1.44, 2.57) and 1.36 (1.13, 1.63) in women with PE and GH respectively. Kaplan–Meier curves of survival time to development of chronic kidney disease revealed that women with preeclampsia were susceptible to kidney function impairment earliest, followed by those with gestational hypertension.

**Conclusions:** There was an increased subsequent risk of CKD associated with hypertensive disorders of pregnancy. Women with GH and PE were also found to have CKD earlier than normotensive women.

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## 1. Introduction

Pre-eclampsia, the symptom complex of high blood pressure and proteinuria, affects 4–8% of pregnancies [1]. It is a multi-system disorder and its effects on subsequent cardiovascular health of women [2,3] are well established. Pre-eclampsia is associated with acute kidney function impairment [4,5] with recovery typically occurring within six weeks of delivery of the baby. Relatively little is known about the long term effects on the kidney

either in terms of physical damage measured by albuminuria or proteinuria, function impairment measured by reduction in Glomerular Filtration Rate (GFR) or end stage kidney failure.

In their systematic review and meta-analysis, McDonald et al. [6] identified 7 papers reporting on a total of 273 patients with preeclampsia and less than 100 events of microalbuminuria. Despite the limited numbers, they found evidence of an increased risk of microalbuminuria following preeclampsia {pooled risk ratio of 4.3 (95% CI 2.7, 6.9)} but there was considerable heterogeneity among the included studies and a strong possibility of publication bias. There was, however, no difference in terms of serum creatinine levels and estimated Glomerular Filtration Rate (eGFR) between women with preeclampsia and those without. An updated search of the literature identified three additional papers [7–9] all reporting a positive association between preeclampsia

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and long term kidney damage, although heterogeneity in terms of exposure and outcome measurement remained as did the possibility of publication bias. In their review, McDonald et al. [6] called for further research investigating the persistence of microalbuminuria following preeclampsia in larger population based studies, taking into consideration confounding factors such as age, BMI, smoking etc.

The overall aim of this research, was to assess the long term effects of hypertensive disorders of pregnancy on kidney function in, using a large phenotypically well-defined population based cohort of women and adjusting for a large number of confounders. In case of declining renal function, we also aimed to find out whether there was a difference in the timing of onset of any decline.

## 2. Methods

### 2.1. Data sources and record linkage

The Aberdeen Maternity and Neonatal Databank (AMND), started in 1950, is derived from the Aberdeen Maternity Hospital's obstetric records. Aberdeen Maternity Hospital is the only maternity hospital in Aberdeen and serves as both a primary as well as tertiary care unit. From the AMND, we identified a cohort of women using the following inclusion and exclusion criteria:

#### 2.1.1. Inclusion criteria

Primiparous mothers born on or before the 30th June 1969 (aged 40 years or over at the end date of the study period with a singleton first delivery occurring at or beyond 20 weeks gestation (including still births) and resident in the Grampian region.

#### 2.1.2. Exclusion criteria

women with pre-existing chronic hypertension, kidney disease as recorded in AMND by ICD-9 codes at the time of the first pregnancy; women who had twins or multiple foetuses in their first pregnancy; women who were temporary residents, living in Orkney or Shetland or elsewhere outside of the Grampian region and women with any delivery with a gestation of less than 20 weeks were excluded from the cohort.

The following databases were linked to the AMND to derive information on outcomes for the end of the study follow up period – 31st July 2009:

- (1) The Grampian Renal Biochemistry Dataset (GRBD) is an existing extract of NHS Grampian's Biochemistry Dataset (1999–2009). All biochemistry services (in-patient, community, private) in the Grampian region were provided by two linked National External Quality Assessment Service monitored laboratories. Data were extracted from the GRBD for women in the AMND cohort who:
  - had renal function tested at least one year after the date of delivery
  - were still living in the Grampian region after 1st July 1999
- (2) The Scottish Morbidity Record for non-obstetric and non-psychiatric general acute inpatient and day case discharges from NHS hospitals in Scotland (SMR01) was introduced in 1961. This was used to identify any hospital admissions from kidney diseases coded according to International Classification of Diseases (10th revision) codes.
- (3) The Scottish Renal Registry (SRR) is a national registry of patients on long term renal replacement therapy. All NHS renal units contribute fully to this database. Data from Scottish renal units were available from 1960 when regular and routine renal replacement therapy (RRT) for end stage renal disease (ESRD) started in Scotland.

- (4) National Records of Scotland (NRS) Data on Deaths (formerly the General Register Office for Scotland (GROS)) – Data collection in this register dates back to 1855. This register was used to identify any deaths occurring in the cohort.

The AMND and GRBD datasets were linked by deterministic matching of the Community Health Index (CHI) numbers, numbers unique to patients registered with a general practice in Scotland. CHI numbers of linked women were validated against the vital status register to identify any deaths or migrations out of Grampian region before 1st July 1999. Linkage of the AMND cohort to the Scottish Morbidity Records (SMR01), death registrations (NR Scotland) and the Scottish Renal Registry was carried out by the Information Services Division (ISD) of NHS Scotland using both deterministic matching on CHI numbers and probability matching using surname, initial of first name, date of birth and post code.

### 2.2. Study design

A cohort study design was used where women who had gestational hypertension (GH) or preeclampsia/ eclampsia (PE) as identified from the AMND formed the exposed cohort, while women who were normotensive (NT) in their first pregnancy constituted the comparison group.

### 2.3. Definition of exposure

Gestational hypertension and preeclampsia were defined according to the criteria proposed by Davey and MacGillivray [10] and used uniformly throughout the AMND. Gestational hypertension was defined as diastolic pressure greater than 90 mmHg on two occasions at least four hours apart or a single reading of >110 mmHg; from 20 weeks gestation onwards in a previously normotensive woman. Pre-eclampsia was defined as gestational hypertension plus at least one episode of proteinuria of 0.3 g/24 h. Eclampsia was defined clinically as convulsions occurring in the presence of pre-eclampsia. In this analysis, women with preeclampsia and eclampsia were considered together as one group.

### 2.4. Outcomes

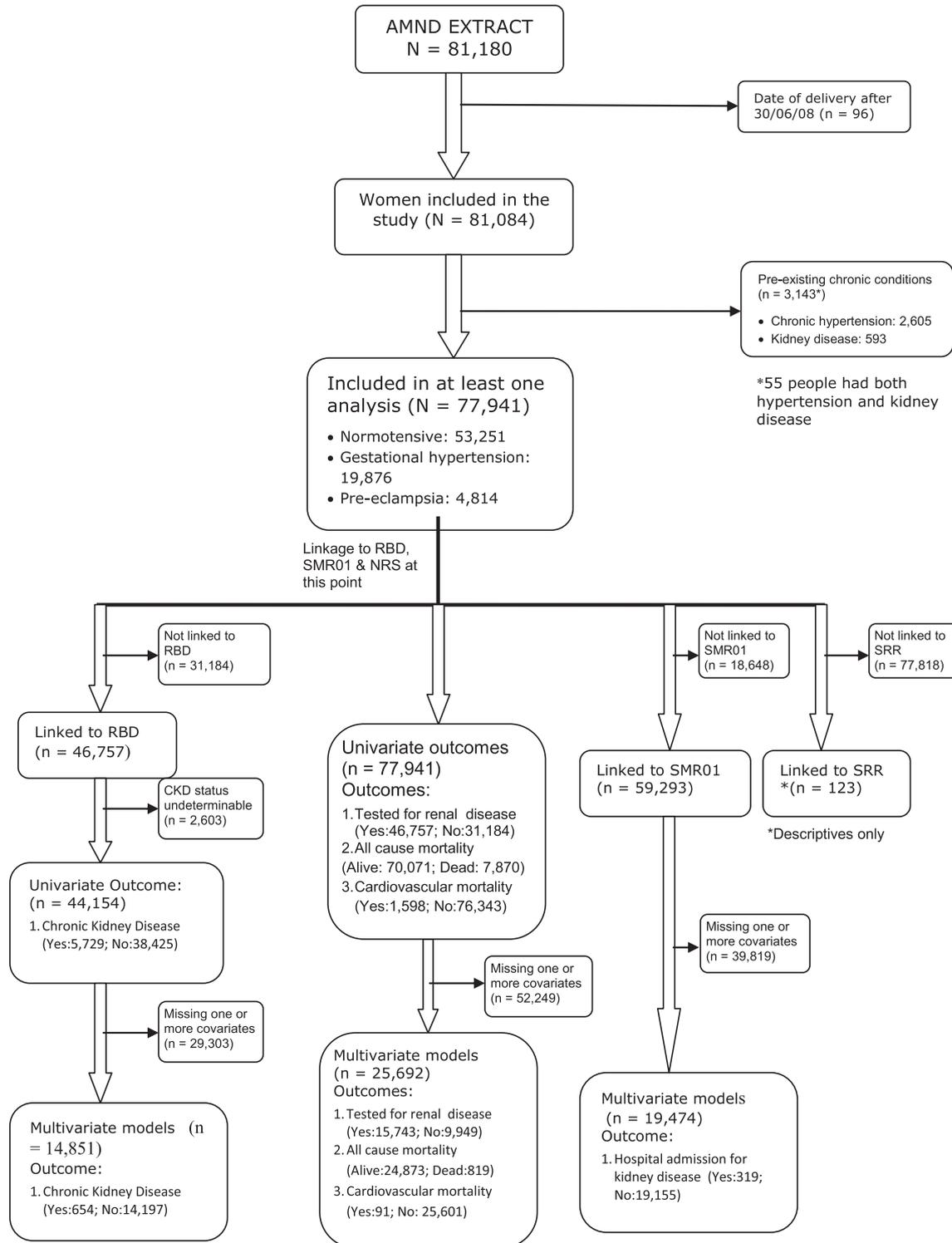
The main outcome of interest was chronic kidney disease defined according to the NICE modified Kidney Disease Outcomes Quality Initiative (KDOQI) definitions for the classification of chronic kidney disease based on renal function measured by glomerular filtration rate (GFR) [11]. Renal function was assessed using serum creatinine values determined by the Jaffe method traceable over time to the international gold standard isotope dilution mass spectrometry (IDMS) method. It was expressed as estimated Glomerular Filtration Rate (eGFR) calculated using the modified 4 variable Modification of Diet in Renal Disease (MDRD) equation suitable for use with IDMS traceable creatinine values. According to these criteria, chronic kidney disease was present if eGFR <60 mL/min/1.73 m<sup>2</sup> sustained for ≥90 days. Proteinuria, a measure of renal damage, was defined using urinary protein creatinine ratio (PCR) and albumin creatinine ratio (ACR) as per SIGN guidelines [12] and classified as chronic if sustained for ≥90 days. We defined women to have CKD if they met either of these criteria in line with KDIGO stage CKD 1–5.

### 2.5. Statistical analysis

Baseline characteristics were examined for women with GH or PE and compared with those who were normotensive (NT) in their first pregnancy. Results were presented as means (and standard

deviation) for continuous variables and frequencies (and percentages) for categorical variables. Pair-wise comparisons were done using independent samples *t*-test for normally distributed

continuous variables and chi squared tests for categorical variables as appropriate. Odds ratios for the primary outcomes (having a subsequent renal function test and development of CKD) were



AMND: Aberdeen Maternity and Neonatal Databank  
 RBD: Renal Biochemistry Database  
 NRS: National Records of Scotland Data on Deaths  
 SMR01: Scottish Morbidity Records for General / Acute Inpatient and Day Case  
 SRR: Scottish Renal Registry records for end stage chronic kidney disease  
 CKD: Chronic Kidney Disease

Fig. 1. Flow chart showing number of women included in analysis for each outcome.

calculated using logistic regression and adjusted ratios with 95% confidence intervals were calculated adjusting for age at first delivery, socio-economic status, smoking status, and body mass index (BMI) at first pregnancy.

Time to CKD was examined using survival analysis techniques. Kaplan-Meier plots and log-rank tests were employed as univariate test for between group differences (pair-wise) in survival from CKD. Cox's proportional hazards models were employed to calculate hazard ratios between groups adjusting for age at first delivery, socio-economic status, smoking status, and BMI.

## 2.6. Ethics Statement

The North of Scotland Research Ethics Service confirmed that formal ethical approval was not necessary to carry out analysis on anonymized data. Permissions to carry out the study were obtained from the steering committee of the Aberdeen Maternity and Neonatal Databank, the NHS Grampian Caldicott guardian, the Privacy Advisory Committee of NHS Scotland and the steering committee for the Scottish Renal Registry.

**Table 1**

Baseline (at time of delivery) characteristics by exposure status.

Characteristics	Normotensive (n = 10,457)	Gestational hypertension (n = 3583)	p value	Pre-eclampsia (n = 811)	p value
Age, mean (SD) years	25.3 (5.3)	25.0 (5.0)	<0.001	24.8 (5.3)	<0.001
Socio-economic status, n (%)			<0.001		0.001
Most affluent I	1088 (10.4)	344 (9.6)		69(8.5)	
II	1694 (16.2)	559 (15.6)		125(15.4)	
III	4821 (46.1)	1727 (48.2)		395 (48.7)	
IV	1955 (18.7)	659(18.4)		154 (19)	
Least affluent V	899 (8.6)	290 (8.1)		68 (8.4)	
Smoking status, n (%)			0.082		0.007
Non smoker	5887 (56.3)	2060 (57.5)		470(57.9)	
Ex smoker	398 (3.8)	129 (3.6)		21 (2.6)	
Current smoker	4172(39.9)	1394 (38.9)		320(39.5)	
BMI, mean (SD) kg/m <sup>2</sup>	23.6 (3.6)	24.9 (4.1)	<0.001	25.3 (4.7)	<0.001

\*p values represent a test for trend

**Table 2**

Logistic models with odds ratios for Chronic Kidney Disease; and Survival models with unadjusted and adjusted hazard ratios for Chronic Kidney Disease, hospital admissions and mortality (all cause and cause specific).

	N of events/N (%)	Unadjusted Odds ratio	95%CI for Odds ratio		p value	Adjusted <sup>a</sup> Odds ratio	95% CI Odds ratio		p value
			Lower	Upper			Lower	Upper	
CKD, n = 14,851									
Normotensive	405/10457 (3.9)	1				1			–
Gestational Hypertension	188/3583 (5.2)	1.37	1.15	1.64	<b>&lt;0.001</b>	1.36	1.14	1.63	<b>0.001</b>
Pre-eclampsia	61/811 (7.5)	2.02	1.53	2.67	<b>&lt;0.001</b>	1.92	1.45	2.56	<b>&lt;0.001</b>
N of events/N (%)									
		Unadjusted Hazard ratio	95%CI for Hazard ratio		p value	Adjusted <sup>a</sup> Hazard ratio	95% CI Hazard ratio		p value
			Lower	Upper			Lower	Upper	
CKD, n = 14,851									
Normotensive	405/10457 (3.9)	1			–	1			–
Gestational Hypertension	188/3583 (5.2)	1.31	1.10	1.55	<b>0.002</b>	1.14	0.96	1.36	0.139
Pre-eclampsia	61/811 (7.5)	1.70	1.30	2.23	<b>&lt;0.001</b>	1.58	1.20	2.07	<b>0.001</b>
Hospital admissions for kidney disease, n = 19,474									
Normotensive	213/13989 (1.5)	1			–	1			–
Gestational Hypertension	82/4482 (1.8)	1.08	0.84	1.40	0.541	1.02	0.78	1.32	0.890
Pre-eclampsia	24/1003 (2.4)	1.42	0.93	2.17	0.101	1.37	0.90	2.10	0.150
All cause death, n = 25,692									
Normotensive	562/18574 (3.0)	1			–	1			–
Gestational Hypertension	197/5857 (3.4)	0.99	0.84	1.16	0.894	0.96	0.82	1.13	0.648
Pre-eclampsia	60/1261 (4.8)	1.37	1.05	1.79	<b>0.020</b>	1.39	1.06	1.81	<b>0.017</b>
Cardiovascular deaths, n = 25,692									
Normotensive	52/18574 (0.3)	1			–	1			–
Gestational Hypertension	29/5857 (0.5)	1.56	0.99	2.46	0.056	1.38	0.87	2.21	0.170
Pre-eclampsia	10/1261 (0.8)	2.53	1.28	4.99	<b>0.007</b>	2.33	1.17	4.64	<b>0.016</b>

Statistically significant p values are shown as bold.

<sup>a</sup> Adjusted for age at delivery, BMI, socio-economic status and smoking status.

## 3. Results

A total of 14,851 women who had been linked to one or more of the databases recording chronic kidney disease status and had complete information regarding age, socio-economic class, smoking and body mass index (BMI) were included in a multivariate model. Of these, 811 had PE, 3583 had GH and 10,457 were normotensive in their first pregnancy (see Fig. 1).

### 3.1. Baseline comparisons

Table 1 presents comparison of baseline characteristics at the time of first pregnancy by exposure status. Women with GH or PE had a lower mean age when compared to normotensive women at the time of delivery. Women with GH or PE also had significantly higher mean BMI in comparison with NT women and were more likely to have chronic hypertension, kidney disease, diabetes. Those with chronic hypertension or CKD at baseline were excluded from further analysis. A lower proportion of women with GH and PE were in the higher socioeconomic classes when compared with

NT women. There was no significant difference in the proportion of women in the smoking categories between women with GH and NT women but women with PE had significantly lower proportions of women who had ever smoked (current and ex-smokers) compared with NT women.

### 3.2. Probability of developing chronic kidney disease

Table 2 presents univariate and multivariate logistic regression models for odds of developing subsequent CKD for women in the three groups with complete information for all covariates in the multivariate model ( $n = 14,851$ ). Compared with normotensive women, women with GH (OR = 1.37, 95%CI 1.15, 1.64) or PE (OR = 2.02, 95%CI 1.53, 2.67) had statistically significantly higher odds of developing subsequent CKD on univariate examination. Adjusted odds ratios were 1.36 (95%CI 1.14, 1.63), and 1.92 (95%CI 1.45, 2.56), for women with GH and PE respectively (adjusted for age and year at delivery, BMI, socio-economic status and smoking status). Again, in both analyses, there was evidence of a “dose response” with OR greater in PE than GH.

### 3.3. Timing of onset of kidney function decline

The survival curves shown in Fig. 2 illustrate the time to development of CKD for women in the different exposure groups as first recorded in the RBD. Women were censored at death or, using the more conservative approach (as compared to the previous model), at last measurement if no further measurement of their kidney function was recorded. The log rank  $p$  values represent pair-wise comparisons between women with GH or PE and NT women. The survival curves for women with GH or PE were significantly different from that of NT women ( $p < 0.001$  in each case).

Table 2 presents survival models with unadjusted and adjusted hazard ratios for chronic kidney disease, hospital admissions for kidney related conditions and all cause and cause specific mortality. Compared to normotensive women, women with PE had a higher risk of developing CKD {AHR 1.58 (95% CI 1.20–2.07)} of all cause mortality {AHR 1.39 (95% CI 1.06–1.81)} and death from

cardiovascular disease {AHR 2.33 (95% CI 1.17–4.64)}. There was no statistically significant difference in hospital admissions from kidney disease. Women with GH did not differ in terms of CKD, hospital admissions from kidney disease and all cause and cause specific mortality from NT women.

## 4. Discussion

On analysis of a large linked dataset with complete information on co-variables, there appears to be a positive association between gestational hypertension as well as preeclampsia with CKD both in univariate as well as multivariate models. Further, women who had gestational hypertension or preeclampsia were at risk of developing CKD earlier than normotensive women.

The study used high quality data on a large population based cohort analysing approximately 2.5 million person years of follow up with 811 women with preeclampsia. We have also used consistent definitions of exposure and outcomes and incorporated the broadest definition of CKD using both proteinuria and eGFR. The linkage with different registers has enabled cross validation of data. We acknowledge possible selection bias arising out of restricting the study to women born before 1969. We also acknowledge that different follow-up times for the different registers meant that some women's outcome could not be adequately classified. We have already acknowledged the uncertainty in the timing of the first diagnosis of CKD for some women because the biochemistry database only started in 1999. Furthermore, we had no information on those women who remained unlinked to all registers, possibly excluding healthy women from our analysis.

Previous reports including a meta-analysis [6] have consistently found associations between PE and CKD. The few studies that have looked at GH and CKD have mostly reported positive associations [13–15] with the notable exception of Gordin [16], who did not find an increased risk of diabetic nephropathy in women with gestational hypertension. There was considerable variation in the definition of GH, PE and CKD in the literature. Most studies have used microalbuminuria as the outcome measure, both as continuous as well as a dichotomous variable. There were less consistent

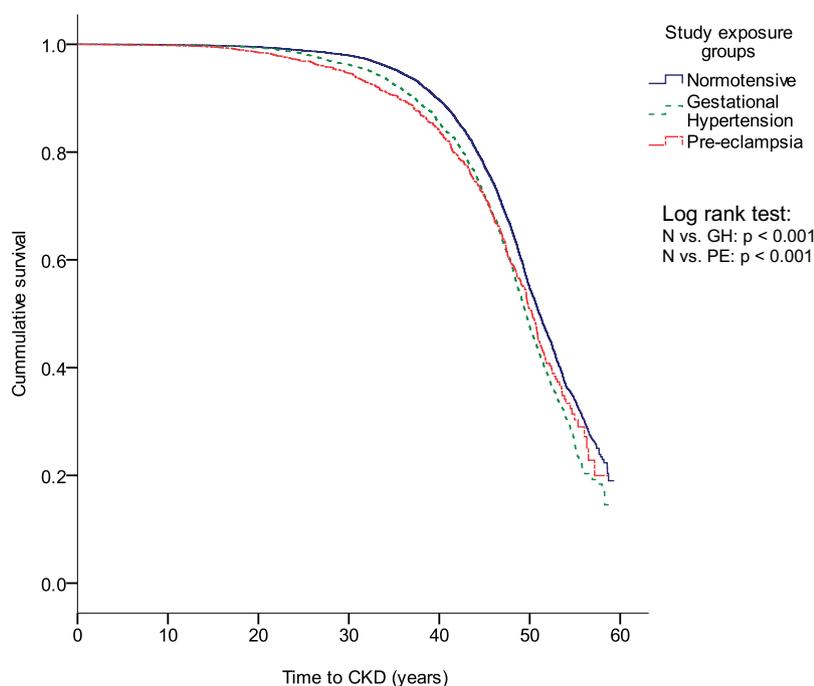


Fig. 2. Kaplan-Meier plot showing survival (time to CKD) curves for three study groups.

associations observed between PE and higher levels of protein in the urine (proteinuria: >300 mg/24 h of protein detected in urine), abnormal biochemistry blood tests (elevated creatinine or reduced glomerular filtration rate (GFR)), abnormal renal biopsy or end stage renal disease (ESRD) [7–9,13]. The largest, and most recently published study [9], used record linkage of the Norwegian Birth and Renal Registries to study the association of PE with Renal Replacement Therapy (RRT). They found that PE in the first pregnancy was associated with an increased relative risk for RRT of 4.7 (95% CI 3.6, 6.1). The relative rarity of RRT meant that even a large population based study like this could only identify 477 cases, assessing only the severe end of the spectrum. McDonald's meta-analysis [6], identified only 273 patients with preeclampsia and less than 100 events of microalbuminuria across a total of 7 cohort studies. In contrast to the existing literature, our findings suggest that the increase in the risk of developing milder CKD in women with hypertensive disorders of pregnancy is likely to be small. In support of this, Jacquemyn [17] did not find an association between HELLP syndrome and long term renal complications.

## 5. Conclusions

Our analyses showed a statistically significantly increased relative risk of CKD in women with GH and PE compared to normotensive women with a possible 'dose response effect'. However the absolute risk of CKD in GH and PE was very low (0.7% and 1.3% over 2.5 million person years of follow up). Therefore, the study demonstrates an effect, a biological pathway whereby GH and PE affect renal function in the longer term but the absolute risk of this happening is very low and therefore is probably not of sufficient clinical importance to warrant any intervention or screening. If a hypothetical intervention was put in place that reduced CKD by 50% in women with PE then the numbers needed to treat (NNT) to prevent one CKD event would be around 150 (Inverse of the absolute risk difference). Similarly, for GH, the NNT would be approximately 285 women with GH. CKD occurs slightly earlier in those with GH and PE, but our study had long follow up times and large numbers of participants resulting in statistically significant effects (type 1 error) which is of interest in terms of mechanisms of disease occurrence, but probably of small clinical relevance.

Currently women with GH and PE are reviewed within 2 months postpartum to ensure that hypertension and proteinuria have resolved, but no specific advice is given regarding long term follow up of renal function [18]. There appears to be a small but significant increased risk of CKD in women with preeclampsia. This implies that alongside managing risk of cardiovascular disease in women with PE and GH, there is also a need to consider long term kidney function. The same lifestyle and risk factor modifications should apply – healthy diet, physical activity, maintaining healthy weight, smoking cessation, cholesterol reduction and blood pressure management.

## Contributorship

DA analysed the data and wrote the first draft of the paper, EA reviewed the literature and helped with statistical analysis, CB, SB, GP and WCS conceived of the research idea and designed the study, SB was responsible for overall supervision. CB, AM and CM helped with the clinical interpretation of the findings, GJP supervised statistical analysis, KW was responsible for data extraction and linkage, SJH facilitated data linkage. All authors contributed to the writing of the final draft of the paper. SB is the guarantor of this paper.

## Ethics statement

Permissions to carry out the study were obtained from the steering committees of the Aberdeen Maternity and Neonatal Databank (SB/SMC/AMND10 dated 08.10.2010), and the Scottish Renal Registry the NHS Grampian Caldicott guardian (dated 20.04.2011), the Privacy Advisory Committee of NHS Scotland (42/11 dated 07/10/2011). Formal ethical approval was not considered necessary by North of Scotland Research Ethics Service as only anonymised data were analysed in this study.

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## Disclosure of interests

The authors declare that they have no conflict of interests

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