

SUPPLEMENTARY MATERIAL

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Data Sources

Since 1968, the Danish Civil Registration System has assigned a unique personal identification number to all Danish residents and continuously updates demographic, vital status and kinship information.^{1,2} Patient contacts with the national healthcare system are registered using the personal identification number, which permits the conduct of record-linkage studies based on Danish health register data with very little loss to follow-up. The National Patient Register contains information on all hospital discharge diagnoses assigned since 1977 and all outpatient diagnoses assigned since 1995.³ Diagnoses are coded in accordance with the International Classification of Diseases (ICD) 8th revision (ICD-8) from 1978-1993 and 10th revision (ICD-10) from 1994 onwards.³ The Causes of Death Register has recorded death certificate information, including underlying and contributing causes of death, since 1970.⁴ The Medical Birth Register contains detailed information on all live births and stillbirths in Denmark since 1973, with gestational length at delivery in completed weeks from 1978.⁵ The Register of Medicinal Product Statistics contains individual-level data on all prescriptions filled in Denmark since 1994.⁶ Registered information includes the amount and dose of dispensed medication and the product's Anatomic Therapeutic Chemical (ATC) code, linked to the personal identification number recorded on the prescription.

International Classification of Diseases (ICD) and Anatomic Therapeutic Chemical (ATC) Codes Used to Define Exclusion Diagnoses, Hypertensive Disorders of Pregnancy, and Kidney Disease

Exclusion diagnoses (National Patient Register)

Congenital or hereditary conditions associated with kidney defects or kidney disease (registered at any time during the study period):

ICD-8: 273.80, 282.09-282.99, 747.69, 747.89, 747.99, 753.09-753.99, 756.89, 759.89

ICD-10: D56.0-D58.9, N07.0-N07.9, N25.1, P96.0, Q27.1, Q27.2, Q60.0-Q63.9, Q87.2, Q87.8

Conditions known or suspected to be related to both hypertensive disorders of pregnancy and kidney disease (registered before a woman's first delivery in the study period or up to 3 months thereafter):

Selected cardiovascular diseases:

ICD-8: 390.09-398.99, 410.09-438.99, 440.09-442.99, 443.09-448.09, 450.99, 452.99-453.09, 456.00-456.09

ICD-10: I70.0-I72.9, I73.1, I73.8, I73.9, I74.0-I74.9, I77.0-I77.9, I78.0, I78.8, I78.9, I79.0-I79.9, I81.0-I82.9, I85.0-I85.9

Hypertension:

ICD-8: 400.09-404.99

ICD-10: I10.0-I15.9

Diabetes mellitus:

ICD-8: 249.00-250.09

ICD-10: E10.0-E14.9

Diseases with autoimmune and/or inflammatory components:

ICD-8: 135.99, 136.01, 136.02, 242.00-242.09, 245.03, 255.10-255.11, 269.00, 274.00-274.09, 281.00-281.09, 283.90-283.92, 287.09, 287.10, 340.00-340.09, 348.09, 354.00, 366.02, 446.09-446.39, 446.91, 446.92, 563.00-563.19, 569.04, 571.90, 693.09, 694.00, 694.02, 694.05, 695.29, 695.49, 696.09-696.19, 701.01, 701.08, 701.09, 709.01, 712.09-712.59, 716.09, 716.19, 733.09, 733.90, 734.00-734.90
ICD-10: D51.0, D59.0, D59.1, D69.0, D69.3, D86.0-D86.9, E05.0, E06.3, E27.1, E27.2, G12.2G, G35.0-G35.9, G61.0, G70.0, H44.1B, K50.0-K51.9, K74.3, K90.0, L10.0, L10.2, L12.0-L12.9, L13.0, L40.0-L40.9, L52.0-L52.9, L80.0-L80.9, L93.0-L93.9, L94.0, L94.1, L94.3, M02.3, M05.0-M06.9, M08.0-M08.4, M08.8, M08.9, M10.0-M11.9, M14.0-M14.9, M30.0, M30.3, M31.0, M31.3-M31.6, M31.1B, M32.0-M34.9, M35.0, M35.2, M35.3, M45.0-M45.9, M72.0

Other conditions increasing the risk of kidney disease:

Renal sequelae of infectious diseases: ICD-8, 019.20, 067.59; ICD-10, A98.5, B52.0, B90.1

Malignant, benign or unknown neoplasm of kidney or pelvis renalis: ICD-8, 223.09, 223.19, 237.39, 237.49; ICD-10, C64.0-C65.9, D30.0, D.30.1, D41.0, D41.1

Antiphospholipid syndrome and other specified coagulation defects: ICD-10, D68.6

Amyloidosis: ICD-8, 276.00-276.09; ICD-10, E85.0-E85.9

Selected nerve disorders and neuropathies: ICD-10, G53.2, G63.2, G63.3, G63.5, G99.0

Post-procedural renal failure: ICD-10, N99.0

Injury to the renal blood vessels, kidney, or unspecified pelvic organ: ICD-8, 866.99, 901.22; ICD-10, S35.4, S37.0, S37.9

Kidney transplantation and complications thereof: ICD-8, 997.70; ICD-10, T86.1, Z94.0

Acquired absence of kidney: ICD-10, Z90.5

Dependence on renal dialysis: ICD-10, Z99.2

Hypertensive disorders of pregnancy (HDP) (National Patient Register)

As registered in the National Patient Register, gestational hypertension is defined as hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) without accompanying proteinuria (ICD-8 code 637.00, ICD-10 codes O13.9 or O16.9). In moderate preeclampsia, mild/moderate hypertension is accompanied by proteinuria (ICD-8 codes 637.03, 637.09 or 637.99, ICD-10 codes O14.0 or O14.9). Severe preeclampsia fulfills the criteria for moderate preeclampsia, with the addition of one or more of the following: severe hypertension, severe proteinuria, signs of organ failure (including the HELLP [hæmolysis, elevated liver enzymes, and low platelets] syndrome), or generalized seizures (ICD-8 codes 637.04, 637.19, 762.19, 762.29, or 762.39, ICD-10 codes O14.1, O14.2, or O15.0-15.9). We categorized eclampsia and the HELLP syndrome with preeclampsia because these conditions are rare in Denmark and there were too few affected women to allow for separate groups.

Kidney disease (National Patient Register and Causes of Death Register)

Registered from 3 months after the first pregnancy in the study period, excluding the period from 20 weeks' gestation to 3 months after delivery in any subsequent pregnancy.

Functional diagnoses

Acute kidney failure: ICD-10, N17.0-N17.9

Chronic kidney disease: ICD-10, N18.0-N18.9

Hypertensive kidney disease: ICD-8, 400.39, 403.99, 404.99; ICD-10, I12.0-I13.9, I15.0, I15.1

Unspecified kidney disease: ICD-8, 636.09; N19.0-N19.9, Z99.2

Etiologic diagnoses

Glomerular and proteinuric disease: ICD-8, 580.00-583.09, 593.27, 636.00, 636.01, 789.09; ICD-10, N01.0-N08.9

Acute tubulointerstitial nephritis: ICD-8, 590.10, 590.11, 593.19, 636.03; ICD-10, N10.0-N10.9

Chronic tubulointerstitial nephritis: ICD-8, 590.09, 593.20; ICD-10, N11.0-N11.9

Unspecified tubulointerstitial nephritis: ICD-8, 590.12, 590.15, 590.19; ICD-10, N12.0-N12.9

Other kidney disease: ICD-8, 584.99, 590.14, 590.20, 590.21, 590.29, 590.99, 593.09, 593.22-593.26, 593.29, 593.50-593.52, 593.59; ICD-10, N15.0-N16.9, N25.0-29.9, O26.8C

Competing causes of kidney disease

Obstructive uropathy: ICD-8, 590.13, 591.00-591.09, 593.33, 593.34; ICD-10, N13.0-N13.9

Nephropathy due to external toxicity: ICD-10, N14.0-N14.9

Diabetic kidney disease: ICD-8, 249.02, 250.02; ICD-10, E10.2, E11.2, E13.2, E14.2

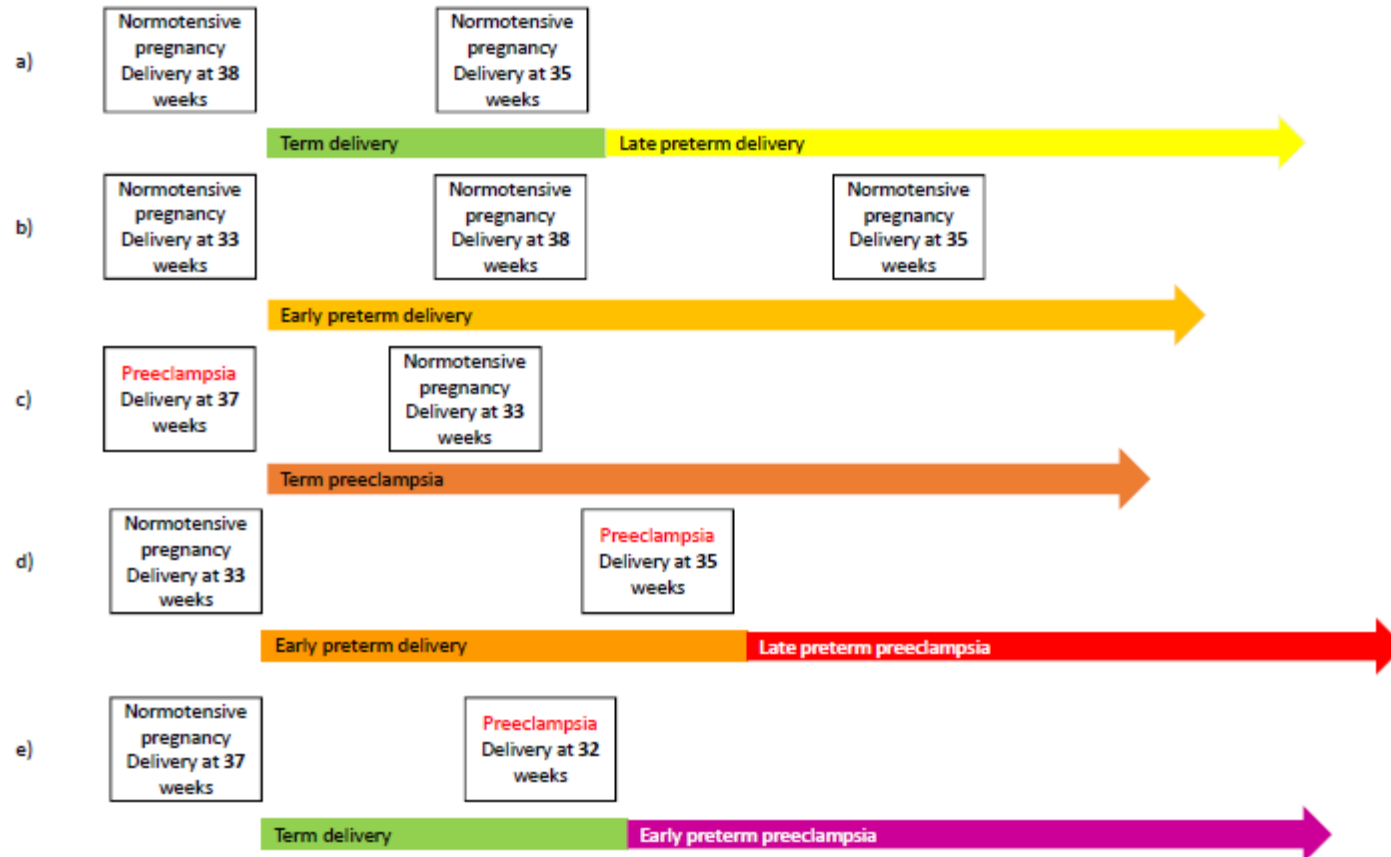
Covariate Definitions

We obtained information on maternal birth year and age from the Civil Registration System and information on parity and stillbirth from the Medical Birth Register. Information on diabetes, cardiovascular disease, and autoimmune/inflammatory disease with debut after the first registered pregnancy was obtained from the National Patient Register, with a woman considered to have the condition from the first registration of that condition (see the definitions of exclusion conditions above for the relevant ICD codes).

As a proxy for incident post-pregnancy hypertension, we used the National Prescription Register to identify women initiating use of anti-hypertensive medication (Anatomic Therapeutic Chemical codes C02, C03, C04, C05, C07, C08, C09) after their first pregnancy in the study period. Initiation of medication use was defined as registration of two filled prescriptions for an anti-hypertensive medication within a 6-month period, without previous use of the medication. Anti-hypertensive medication use that was potentially related to HDP treatment (use from 20 weeks before delivery to three months postpartum) was ignored when determining whether, and when, medication use was initiated.

With the exception of anti-hypertensive medication use, information on potential confounders was available from 1978 onward. Anti-hypertensive medication use data was first available in 1994; therefore, adjustment for hypertension and the mediation analyses involving hypertension occurred only in a sub-cohort of women. Parity, maternal age, diabetes, cardiovascular disease, and hypertension were treated as time-dependent variables. Women with filled prescriptions registered in 1994 were considered prevalent (current) users of anti-hypertensive medications and excluded from the sub-analyses that included hypertension.

Supplementary Figure A. Follow-up time for the stratification variable was classified according to the length of a woman's shortest pregnancy at a given point in time. Her first pregnancy was classified as an early preterm delivery (<34 weeks), a late preterm delivery (34-36 weeks), or a term delivery (≥37 weeks). If a subsequent pregnancy put her in an earlier delivery category, follow-up time was assigned to that category from that point onwards (a), whereas if subsequent pregnancies ended at the same point or later, her delivery category did not change (b). However, the length of a preeclamptic pregnancy superceded the length of any normotensive pregnancy, even a normotensive pregnancy ending in early preterm delivery (c, d, and e).



Supplementary Table A. Hazard ratios for unspecified and other kidney disease by history of preeclampsia (PE) and timing of delivery, Denmark, 1978-2015.

Timing of delivery	History of PE	Unspecified tubulointerstitial nephritis					
		Unspecified kidney disease		nephritis		Other kidney disease	
		Number	HR (95% CI)	Number	HR (95% CI)	Number	HR (95% CI)
Early preterm (<34 weeks)	Yes	*	-	*	0.52 (0.16 to 1.67)	10	2.13 (1.06 to 4.26)
	No	13	1 (ref)	49	1 (ref)	39	1 (ref)
Late preterm (34-36 weeks)	Yes	6	2.45 (1.01 to 5.95)	12	1.11 (0.61 to 2.01)	11	1.38 (0.74 to 2.58)
	No	27	1 (ref)	123	1 (ref)	91	1 (ref)
Term (≥37 weeks)	Yes	34	2.03 (1.42 to 2.89)	75	1.20 (0.95 to 1.51)	73	1.32 (1.04 to 1.67)
	No	376	1 (ref)	1,407	1 (ref)	1,246	1 (ref)

CI, confidence interval. HR, hazard ratio.

All hazard ratios are adjusted for maternal age (underlying time in the Cox model), maternal birth year, parity, history of gestational hypertension, and history of shortest gestation.

* Under current Danish and European data protection laws, exact numbers cannot be given because one cell contains less than 5 women.

Supplementary Table B. Hazard ratios for acute and chronic renal disorders by history of preeclampsia (PE) and time since latest pregnancy, Denmark, 1978-2015.

Time since latest pregnancy	History of PE	Person -years (x10 ³)	Acute renal disorders						Chronic renal disorders					
			Acute kidney failure		Acute tubulointerstitial nephritis		Chronic kidney disease		Hypertensive kidney disease		Chronic tubulointerstitial nephritis		Glomerular and proteinuric disease	
			No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)
< 5 years	Yes	321	*	1.30 (0.50 to 3.61)	107	1.03 (0.85 to 1.25)	*	6.11 (3.84 to 9.72)	20	4.65 (2.78 to 7.77)	8	1.47 (0.71 to 3.02)	114	4.77 (3.88 to 5.86)
	No	6,804	54	1 (ref)	2,148	1 (ref)	72	1 (ref)	68	1 (ref)	110	1 (ref)	472	1 (ref)
≥5 years	Yes	584	62	1.38 (1.06 to 1.78)	223	1.14 (1.00 to 1.31)	115	2.06 (1.69 to 2.50)	65	2.94 (2.25 to 3.84)	14	1.62 (0.94 to 2.82)	82	1.50 (1.19 to 1.88)
	No	12,285	873	1 (ref)	3,849	1 (ref)	1,074	1 (ref)	416	1 (ref)	161	1 (ref)	1,086	1 (ref)
P value for difference			0.92		0.38		<0.001		0.12		0.82		<0.001	

CI, confidence interval. HR, hazard ratio.

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