Supplementary material to *Kidney Disease in Women With Previous Gestational Diabetes Mellitus: A Nationwide Register-Based Cohort Study*

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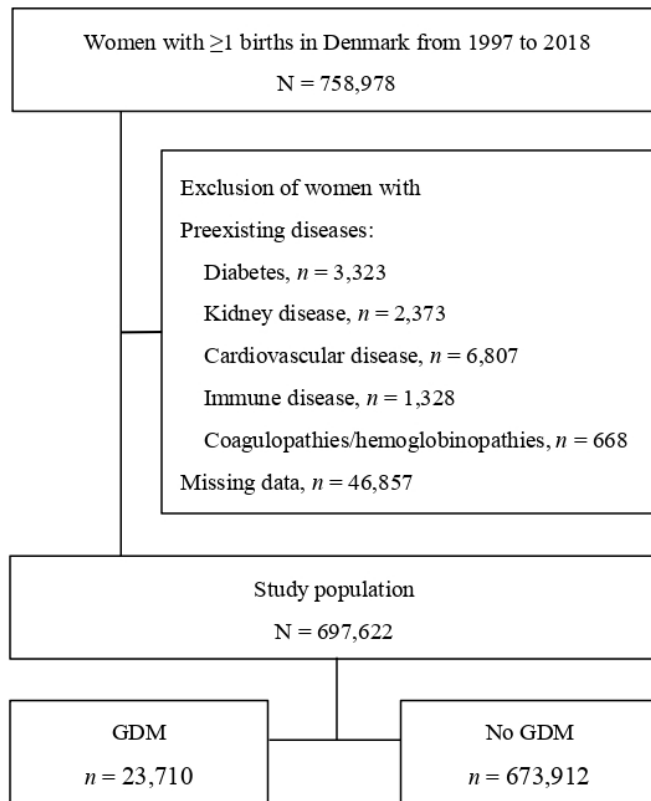
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Supplementary Table S1 – Definitions of variables according to the ICD-10 codes (International Classification of Diseases, 10th revision) and the ATC groups (Anatomical Therapeutic Chemical groups)

	ICD-10 codes and ATC groups
Exclusion criteria	At or 2 years before index date
Preexisting diabetes	ICD-10: E10-E14, O240-O243, O245, O249 *and/or* ATC: A10 (except A10BA02) (≥2 redemptions)
Preexisting kidney disease: Kidney disease Hypertensive kidney disease Congenital malformation and renal failure Kidney transplant/dialysis	 ICD-10: N00-N19 ICD-10: I12-I15.1 ICD-10: P960, Q271-Q272, Q60-Q64, Q878 ICD-10: Z905, Z940, Z992, T861
Preexisting cardiovascular disease	ICD-10: I00-I09, I20-I99, G45-G46
Preexisting immune diseases	ICD-10: D86, L93, M300-M359, M628B, T796D
Preexisting coagulopathies/hemoglobinopathies	ICD-10: D56-D59, D68
Additional exclusion criteria for sensitivity analysis: All conditions listed above All other genitourinary diseases Preexisting hypertension	 All diagnosis codes listed above ICD-10: N20-N29, N31-N39 ICD-10: I10-11, I152-9 (within 2 years prior to index date until gestational week 20) *and/or* ATC: C02-C03, C07-C09 (≥2 redemptions within 2 years prior to index date until gestational week 20)
Exposure	
Gestational diabetes mellitus (GDM)	ICD-10: O244
Outcomes	From 6 weeks postpartum
Chronic kidney disease (CKD) Glomerular and proteinuric disease Chronic tubulointerstitial nephritis Unspecified CKD Hypertensive kidney disease Diabetic kidney disease Renal dialysis Kidney transplant	ICD-10: N01-N08, N11-N12, N15-N16, N18-N19, I12-I151, Z992, Z905, Z940, T861 ICD-10: N01-N08, except N083 ICD-10: N11-N12, N15-N16 ICD-10: N18-N19 ICD-10: I12-I151 ICD-10: E102, E112, E132, N083 ICD-10: Z992 ICD-10: Z905, Z940, T861
Acute kidney disease Acute tubulointerstitial nephritis Unspecified acute renal failure	ICD-10: N10, N17 ICD-10: N10 ICD-10: N17
Covariates	Data from index pregnancy unless stated otherwise
Maternal age	Age in years at date of delivery
Primiparity Parity	No deliveries prior to index pregnancy For confounder adjustment, parity was entered as a time-varying confounder in the Cox regression models
Pregestational BMI	Selfreported data or measured at first antenatal visit
Smoking during pregnancy	Selfreported data
Preexisting hypertension	ICD-10: I10-11, I152-9 (within 2 years prior to index date until gestational week 20) *and/or*

	ATC: C02-C03, C07-C09 (≥2 redemptions within 2 years prior to index date until gestational week 20)
Preexisting dyslipidemia	ICD-10: E78 (within 2 years prior to index) *and/or* ATC: C10 (≥2 redemptions within 2 years prior to index date)
Preexisting PCOS	ICD-10: E282
Preexisting metformin treatment	ATC: A10BA02 (≥2 redemptions within 2 years prior to index date)
Preexisting comorbidity	Based on Charlson Comorbidity Index score
Ethnicity	Combination of data on ethnicity/immigration status and country of origin and divided into four categories:
Danish	Born in Denmark or abroad by parents where at least one parent is born in Denmark and holds Danish citizenship
Immigrant, Western	Born in 'Other Western countries' by parents born outside of Denmark and without Danish citizenship
Immigrant, Non-Western	Born in 'Non-Western countries' by parents born outside of Denmark and without Danish citizenship
Descendant	Born in Denmark by parents that were born outside of Denmark and who do not hold Danish citizenships
Marital status	Combination of data on marital status and family type and divided into two categories (Single/not living with a partner, Married/living with a partner)
Income	In the calendar year prior to delivery based on a format by Statistics Denmark and divided into three categories (Low, Middle, High)
Highest completed education	Based on a format by Statistics Denmark and divided into three categories (Lower secondary, Upper secondary, Post secondary)
Occupation	Based on data on connection to the workforce by Statistics Denmark and divided into four categories (Employed, Unemployed or on welfare payment, Under education, Early retirement)
Preeclampsia	ICD-10: O11, O14 (from gestational week 20 to 6 weeks postpartum)
Gestational hypertension	ICD-10: O13, O16 (from gestational week 20 to 6 weeks postpartum)
Any hypertensive disorder in pregnancy	ICD-10: O11, O13-16 (from gestational week 20 to 6 weeks postpartum)
Preterm delivery	Delivery prior to gestational week 37
Insulin treatment (in any GDM pregnancy)	ICD-10: O244E *and/or* ATC: A10A (≥1 redemption in ≥1 GDM pregnancy)
Proxy of severity of metabolic dysfunction	Increasing severity with category 3 being the most severe
1. No GDM 2. Non-insulin-treated GDM 3. Insulin-treated GDM	No GDM diagnosis in any pregnancy GDM in ≥1 pregnancy, no insulin treatment (see above) GDM in ≥1 pregnancy and insulin treatment (see above)
Mediators	After index pregnancy and prior to outcome
Subsequent diabetes	ICD-10: E10-E14, O240-O243, O245, O249 *and/or* ATC: A10 (≥2 redemptions) *and* no incident outcome prior to subsequent diabetes
Subsequent hypertension	ICD-10: I10-11, I152-159 *and/or* ATC: C02-C03, C07-C09 (≥2 redemptions) *and* no incident outcome prior to subsequent hypertension

Supplementary Figure S2

Women with ≥1 births in Denmark from 1997 to 2018
N = 758,978

Exclusion of women with

Preexisting diseases:

    Diabetes, $n = 3,323$

    Kidney disease, $n = 2,373$

    Cardiovascular disease, $n = 6,807$

    Immune disease, $n = 1,328$

    Coagulopathies/hemoglobinopathies, $n = 668$

Missing data, $n = 46,857$

Study population
N = 697,622

GDM
$n = 23,710$

No GDM
$n = 673,912$

Supplementary Figure S2 – Flowchart of the study population

Supplementary Text S3 – Description and results of the sensitivity analyses

We performed a series of sensitivity analyses. The study population was restricted by excluding women with the following: 1) any deliveries prior to study entry; 2) pregnancy complications that were considered as risk factors for kidney disease (preeclampsia, gestational hypertension, any hypertension during pregnancy, preterm delivery); 3) preexisting hypertension or all diagnosis codes in the complete ICD-10 chapter 14 regarding diseases of the genitourinary system (except ICD-10 N30) within 2 years prior to index date; and 4) missing data on gestational age (rather than using imputation). Then, GDM exposure was restricted by only considering GDM diagnosis after gestational week 20 without the diagnosis code for preexisting diabetes during the same pregnancy. Furthermore, risk time was expanded to include time during pregnancy and up to 6 weeks postpartum and GDM diagnosis date was equated to the index/conception date under the assumption that the GDM diagnosis date preceded the date of kidney disease outcome. Additionally, we generated missing categories for women with missing data for the potential confounders in the main analyses rather than excluding them from the analyses. Finally, the adjustment for confounders in the Cox regression analyses was expanded by supplementing with adjustment for preexisting PCOS/metformin treatment, any pregnancy-related hypertensive disorder (preeclampsia or gestational hypertension), pregestational BMI, and smoking during index pregnancy.

In general, the adjusted risk estimates from the sensitivity analyses differed slightly in both directions compared to the main analysis but did not change the statistical significance (data not shown). However, when we excluded the women experiencing obstetric complications in index pregnancy that were considered as risk factors for future kidney disease (i.e. preeclampsia, gestational hypertension, preterm delivery), the association between GDM and renal dialysis became statistically significant (N=619,414; aHR 2.88 [95% CI 1.31–6.35]) from being insignificant in the main analysis. This interesting finding needs further exploration.

We observed that the association between GDM and the CKD subcategory outcomes of glomerular and proteinuric disease and unspecified CKD became insignificant when the study population was reduced by excluding women with deliveries prior to index delivery (N=540,607) and including pregestational BMI

(N=369,678) in the adjusted model. However, the statistical significance persisted for the overall CKD-composite. The loss of significance for the mentioned CKD subcategories may be attributed to the relatively low number of outcome events in the study population for the sensitivity analyses and the characteristics of the excluded women. The study population was reduced by excluding 1) women with higher parity and hence expectedly higher age and 2) women delivering in the beginning of the study period (i.e., prior to the initiation of registration of pregestational BMI in 2003). Hence, women who were older and had longer follow-up duration during the study period were excluded. These two factors expectedly resulted in the omission of data for a group of women who were more likely to experience outcome events because of higher age and longer follow-up duration and hence belonged to the higher-risk group. This potentially explains in a large part the change in statistical significance. However, it is also plausible that this reflects a true lack of association. When adjusting for pregnancy-related hypertensive disorders (N=694,178), the risk estimates attenuated slightly, e.g., for CKD from 1.92 (95% CI 1.67–2.21) to 1.80 (95% CI 1.57–2.08). However, all associations between GDM and the CKD subcategories remained statistically significant apart from Unspecified CKD where the aHR changed from 1.47 (95% CI 1.09–1.99) to 1.33 (95% CI 0.99–1.80), i.e., significance was just exactly lost after adjustment for pregnancy-related hypertensive disorders (Supplementary Table S5).

Finally, a stricter definition of GDM resulted in the loss of significance regarding the subcategory outcome of unspecified CKD. The restriction of GDM exposure status to diagnosis after gestational week 20 and absence of concurrent registration of the diagnosis code for preexisting diabetes resulted in a shift of the number of events from the exposed group to the unexposed group. This reduced the number of events of unspecified CKD from 46 to 33 events in the GDM group whereby the statistical significance between women with and without GDM disappeared. In hindsight, the classification of women that were diagnosed with GDM prior to gestational week 20 as non-GDM was a highly restrictive strategy. However, the results of this sensitivity analysis did not jeopardize the overall conclusions of this study.

Supplementary Table S4 – Risk of CKD according to GDM in women giving birth in Denmark from 1997 to 2018 after stratification into time periods after delivery

	Overall aHR* (95% CI)	aHR* within 0–2 years (95% CI)	aHR* ≥ 2 years (95% CI)
CKD	1.92 (1.67–2.21)	0.75 (0.37–1.52)	2.04 (1.77–2.36)
Glomerular and proteinuric disease	1.96 (1.42–2.70)	1.53 (0.62–3.78)	2.04 (1.45–2.88)
Chronic tubulointerstitial nephritis	1.16 (0.91–1.49)	– †	1.23 (0.96–1.58)
Unspecified CKD	1.47 (1.09–1.99)	0.74 (0.18–3.04)	1.54 (1.14–2.09)
Hypertensive kidney disease	1.27 (0.69–2.33)	– †	1.35 (0.74–2.49)
Diabetic kidney disease	17.03 (12.66–22.91)	22.98 (1.94–271.94)	16.97 (12.59–22.86)
Renal dialysis	2.00 (0.97–4.15)	– †	2.04 (0.99–4.24)
Kidney transplant	0.96 (0.39–2.35)	– †	1.02 (0.42–2.51)

*Adjusted for age, parity, CCI score, preexisting hypertension, ethnicity, marital status, income, education, occupation, and calendar year of delivery. †Too few observations.

Supplementary Table S5 – Risk of CKD according to GDM in women giving birth in Denmark from 1997 to 2018 after additional adjustment for any hypertensive disorder during pregnancy

	GDM			No GDM				
	n of events	Risk time	IR* (95% CI)	*n* of events	Risk time	IR* (95% CI)	Adjusted HR[†] (95% CI)	Adjusted HR[‡] (95% CI)
CKD§	210	183,288	1.1 (1.0–1.3)	3,789	7,824,700	0.5 (0.5–0.5)	1.92 (1.67–2.21)	1.80 (1.57–2.08)
Glomerular and proteinuric disease	40	185,244	0.2 (0.2–0.3)	791	7,872,790	0.1 (0.1–0.1)	1.96 (1.42–2.70)	1.74 (1.26–2.40)
Chronic tubulointerstitial nephritis	66	185,277	0.4 (0.3–0.5)	1,942	7,870,362	0.2 (0.2–0.3)	1.16 (0.91–1.49)	1.15 (0.90–1.47)
Unspecified CKD	46	185,343	0.2 (0.2–0.3)	1,014	7,874,893	0.1 (0.1–0.1)	1.47 (1.09–1.99)	1.33 (0.99–1.80)
Hypertensive kidney disease	11	185,522	0.1 (0.0–0.1)	298	7,878,261	0.0 (0.0–0.0)	1.27 (0.69–2.33)	1.09 (0.59–2.00)
Diabetic kidney disease	77	185,201	0.4 (0.3–0.5)	136	7,880,044	0.0 (0.0–0.0)	17.03 (12.66–22.91)	15.89 (11.78–21.42)
Renal dialysis	8	185,575	0.0 (0.0–0.1)	118	7,880,073	0.0 (0.0–0.0)	2.00 (0.97–4.15)	1.82 (0.88–3.78)
Kidney transplant	5	185,579	0.0 (0.0–0.1)	167	7,879,687	0.0 (0.0–0.0)	0.96 (0.39–2.35)	0.86 (0.35–2.11)

* Incidence rate (IR) presented as *n* of events per 1,000 person-years. †Adjusted for age, parity, CCI score, preexisting hypertension, ethnicity, marital status, income, education, occupation, and calendar year of delivery. ‡ Adjusted for age, parity, CCI score, preexisting hypertension, ethnicity, marital status, income, education, occupation, calendar year of delivery and any hypertensive disorder during pregnancy §Diagnosis of glomerular and proteinuric disease, chronic tubulointerstitial nephritis, unspecified CKD, hypertensive kidney disease, diabetic kidney disease, renal dialysis, or kidney transplant.