Pregnancy outcomes in women with chronic kidney disease and chronic hypertension: a National cohort study

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BACKGROUND: Maternal chronic kidney disease and chronic hypertension have been linked with adverse pregnancy outcomes. We aimed to examine the association between these conditions and adverse pregnancy outcomes over the last 3 decades.

OBJECTIVE: We conducted this national cohort study to assess the association between maternal chronic disease (CH, CKD or both conditions) and adverse pregnancy outcomes with an emphasis on the effect of parity, maternal age, and BMI on these associations over the last three decades. We further investigated whether different subtypes of CKD had differing effects.

STUDY DESIGN: We used data from the Swedish Medical Birth Register, including 2,788,490 singleton births between 1982 and 2012. Women with chronic kidney disease and chronic hypertension were identified from the Medical Birth Register and National Patient Register. Logistic regression models were performed to assess the associations between maternal chronic disease (chronic hypertension, chronic kidney disease, or both conditions) and pregnancy outcomes, including pre-eclampsia, in-labor and prelabor cesarean delivery, preterm birth, small for gestational age, and stillbirth.

RESULTS: During the 30-year study period, 22,397 babies (0.8%) were born to women with chronic kidney disease, 13,279 (0.48%) to women with chronic hypertension and 1079 (0.04%) to women with both conditions. Associations with chronic hypertension were strongest for pre-eclampsia (adjusted odds ratio, 4.57; 95% confidence interval, 4.33–4.84) and stillbirth (adjusted odds ratio, 1.65; 95% confidence interval, 1.35–2.03) and weakest for spontaneous preterm birth in women with both conditions (adjusted odds ratio, 1.07; 95% confidence interval, 0.96–1.20). The effect of chronic kidney disease varied from (adjusted odds ratio, 2.05; 95% confidence interval, 1.92–2.19) for indicated preterm birth to no effect for stillbirth (adjusted odds ratio, 1.16; 95% confidence interval, 0.95–1.43). Women with both conditions had the strongest associations for in-labor cesarean delivery (adjusted odds ratio, 1.86; 95% confidence interval, 1.49–2.32), prelabor cesarean delivery (adjusted odds ratio, 2.68; 95% confidence interval, 2.18–3.28), indicated preterm birth (adjusted odds ratio, 9.09; 95% confidence interval, 7.61–10.7), and small for gestational age (adjusted odds ratio, 4.52; 95% confidence interval, 3.68–5.57). The results remained constant over the last 3 decades. Stratified analyses of the associations by parity, maternal age, and body mass index showed that adverse outcomes remained independently higher in women with these conditions, with worse outcomes in multiparous women. All chronic kidney disease subtypes were associated with higher odds of pre-eclampsia, in-labor cesarean delivery, and medically indicated preterm birth. Different subtypes of chronic kidney disease had differing risks: strongest associations of pre-eclampsia (adjusted odds ratio, 3.98; 95% confidence interval, 2.98–5.31) and stillbirth (adjusted odds ratio, 2.73; 95% confidence interval, 1.13–6.59) were observed in women with congenital kidney disease, whereas women with diabetic nephropathy had the most pronounced increase odds of in-labor cesarean delivery (adjusted odds ratio, 3.54; 95% confidence interval, 2.06–6.09), prelabor cesarean delivery (adjusted odds ratio, 7.50; 95% confidence interval, 4.74–11.9), and small for gestational age (adjusted odds ratio, 4.50; 95% confidence interval, 2.92–6.94). In addition, women with renovascular disease had the highest increased risk of preterm birth in both spontaneous preterm birth (adjusted odds ratio, 3.01; 95% confidence interval, 1.57–5.76) and indicated preterm birth (adjusted odds ratio, 8.09; 95% confidence interval, 5.73–11.4).

CONCLUSION: Women with chronic hypertension, chronic kidney disease, or both conditions are at an increased risk of adverse pregnancy outcomes which were independent of maternal age, body mass index, and parity. Multidisciplinary management should be provided with intensive clinical follow-up to support these women during pregnancy, particularly multiparous women. Further research is needed to evaluate the effect of disease severity on adverse pregnancy outcomes.

Key words: chronic kidney disease, chronic hypertension, fetal death, fetal outcome, obstetrical outcome, preeclampsia, pregnancy

Introduction

 Chronic kidney disease (CKD) affects up to 3% of pregnant women in developed countries.1 This estimated prevalence is expected to rise owing to increasing maternal age and obesity rates. Previous reports from meta-analysis2–6 and cohort studies2–6 demonstrate that women with CKD have an increased risk of maternal and perinatal complications. A meta-analysis of 14 studies reported greater odds of preeclampsia (PE), cesarean delivery (CD), preterm birth (PTB), and small for gestational age (SGA) or low birthweight in women with CKD than women without CKD.3 However, only 4 of the 14 studies accounted for potential confounders such as maternal age and other comorbidities, and only 6 studies compared women with CKD and healthy pregnant women. The remaining 8 studies enrolled patients with...
comorbidities of diabetes mellitus (diabetic nephropathy as exposed group), which make it difficult to extend the results to the general population of women with other underlying causes of CKD. Moreover, most of the previous studies on CKD represent small, retrospective case series studies that were performed in a single center and were of low methodological quality.2 In addition, the effect size estimates of adverse outcomes vary between cohort studies,7–9 and this heterogeneity might be a result of lumping together different causes of CKD. However, limited studies have focused on pregnancy outcomes in women with specific subtypes of CKD.

Similarly, a substantial number of pregnancies (0.6%–3%) are complicated by chronic hypertension (CH).10,11 Previous systematic review12 and observational studies10,13–18 have linked maternal CH with adverse perinatal outcomes. A recent United Kingdom cohort study reported an increased risk of PE, elective CD, indicated PTB, stillbirth, and SGA in women with CH compared with normotensive women.10 Some adverse perinatal outcomes, such as fetal growth restriction and PTB, are the most important contributors to increased perinatal morbidity and mortality.10–21 However, inconsistency exists among studies that investigated the association between CH and the risk of emergency CD10,13 and spontaneous PTB.17,18 Despite the reported associations between maternal CH and CKD on the risk of adverse pregnancy outcomes, it is not clear whether these outcomes have improved over the last decades.

Piccoli et al5 (2015) reported that CH affects 22% to 54% of pregnant women with CKD, depending on the severity of kidney disease. Although previous studies have assessed the effect of maternal CH and CKD on adverse pregnancy outcomes, the evidence is limited on the combined effect of CKD and CH on adverse pregnancy outcomes and on the effect of CKD subtypes on adverse pregnancy outcomes. The role of maternal age, parity, and obesity in the associations between CKD and CH on adverse pregnancy outcomes is also unclear and requires further exploration in terms of potential confounding and effect modification. We conducted this national cohort study to assess the association between maternal chronic disease (CH, CKD, or both conditions) and adverse perinatal outcomes with an emphasis on the effect of parity, maternal age, and body mass index (BMI) on these associations over the last 3 decades. We further investigated the associations among women with CKD subtypes.

Materials and Methods
Study design, data source, and participants
This nationwide cohort study used data from the Swedish Medical Birth Registry (MBR), which contains prenatal and birth information for nearly all births (>99%) in Sweden since 1973.22 Data were gathered prospectively from the first antenatal visit including demographic information, reproductive history, pregnancy outcomes, and complication during pregnancy, delivery, and antenatal period. All disease and complications during pregnancy or delivery are classified according to the Swedish version of the International Classification of Diseases (ICD), using the eighth revision until 1986, the ninth revision from 1987 to 1996, and the tenth revision since 1997.

The study cohort consisted of all registered births to women who had their first recorded delivery between January 1982 and December 2012. We excluded multiple births to improve internal comparability because multiple gestations have an increased risk of obstetrical complications including intrauterine growth restriction and PTB.23 We also excluded births before 1982 because data were poorly recorded, such as lack of information on maternal smoking and BMI, and to be able to adjust for maternal reproductive history (eg, parity). We also used hospitalization data from the Swedish National Patient Register (NPR), which included inpatient data from 1964 and outpatient data from 2000 onward, to identify women with CH or CKD.24 Data from MBR and NPR registers were linked using the anonymized unique national identification number. Ethical approval was obtained from the Swedish Ethical Review Authority in Stockholm (Regionala Etikprövningsnamnden Stockholm), Sweden, and the Social Research and Ethics Committee, University College Cork (#2019-214).

Exposures
Data on diagnoses of CH and CKD were obtained from the MBR and NPR using ICD codes. Similarly, we further identified the following CKD subtypes:
tubulointerstitial, glomerular/proteinuric, diabetic nephropathy, renovascular disease, congenital/ malformation kidney disease (women with congenital abnormalities of the kidney and urinary tract), and unspecified CKD using ICD codes from MBR and NPR (Supplemental Table 1).

Outcome measures
PE was defined as at least 2 diastolic blood pressure measurements of ≥90 mm Hg, combined with proteinuria (≥0.3 g/day or ≥1+ on a urine dipstick), and this was obtained from primary and secondary maternal diagnoses in the MBR using ICD codes. Prelabor CD and in-labor CD were defined as CD before and after onset of labor, respectively. PTB was categorized as spontaneous PTB (<37 weeks’ gestation) and medically indicated PTB (<37 weeks’ gestation). We further classified PTB into extreme preterm (<28 weeks), severe preterm (28–31 weeks), moderate preterm (32–33 weeks), and near term (34–36 weeks) delivery. Stillbirth (antenatual and intrapartum fetal death) was defined as fetal loss after 28 completed weeks (until June 2008), but that was changed to fetal loss after 22 completed weeks since July 2008. SGA was defined as a birthweight below 2 standard deviations (SDs) of the mean birthweight of the sex-specific and gestational age distributions.

Potential confounders
The following potential confounders were considered in the analysis: maternal age, smoking, BMI, parity, country of origin, asthma, diabetes mellitus, cardiovascular disease, and highest educational level.

Statistical analysis
Data on the maternal and fetal characteristics are presented according to CH and CKD status using frequency and percentages for categorical variables and mean with SD for continuous variables. Crude and adjusted logistic regression models were performed to calculate the odds ratios (ORs) with 95% confidence intervals (CIs) for the association between maternal CKD and CH and each of the adverse pregnancy outcomes.

The exposure variable was represented in the models as a 4-category variable: (1) normotensive women without CKD (reference group), (2) women with CH, (3) women with CKD, and (4) women with CH and CKD. We performed a separate analysis to investigate the effect of different subtypes of CKD on adverse pregnancy outcomes, with the same reference group. In this analysis, separate categories were created for women with CH and for those without information on specific subtypes of CKD.

The potential confounders were included in the models as categorical variables as presented in Table 1, in addition to offspring year of birth. Where there were missing data on smoking during pregnancy and maternal BMI, we added a missing data category in the variable. All analyses of PTB were compared with term babies. For prelabor and in-labor CD, we analyzed each outcome separately compared with spontaneous birth.

We conducted stratified analyses to investigate the associations over 5-year periods from 1982 to 2012 to assess whether the associations changed over time (sensitivity and subgroup analyses are given in Supplemental Material page 2). All analyses were performed using Stata/MP 16.1 (StataCorp LLC, College Station, TX), and P<.05 was considered statistically significant.

Results
This study consisted of 2,788,490 singleton births, from 1,420,846 women, born between 1982 and 2012 (972,136 women had more than 1 birth during the study period); the flow diagram of participants is shown in Supplemental Figure 1. During the study period, 22,397 babies (0.80%) were born to women with CKD, 13,279 babies (0.48%) were born to women with CH, and 1079 babies (0.04%) were born to women with both conditions (CKD and CH). The prevalence of pregnant women with CH and CKD has increased over the last 3 decades (Supplemental Figure 2).

The sociodemographic characteristics of the women are presented in Table 1. Women with CKD, CH or both conditions were older on average and had higher BMI and were more likely to have diabetes mellitus, cardiovascular disease, and asthma, with the highest percentage of comorbidities among women with both conditions. Women with CKD were more likely to be smokers (20%), whereas similar percentages of nonsmokers were found in women with CH and those with a combination of both conditions (84% and 81%, respectively).

Adverse perinatal outcomes among women with chronic hypertension, chronic kidney disease, or both conditions
The ORs for perinatal outcomes are presented in Table 2. After controlling for confounding factors, CH, CKD, or both conditions associated with adverse perinatal outcomes. Women with CH had higher odds of PE (aOR, 4.57; 95% CI, 4.85–6.46), in-labor CD (aOR, 1.70; 95% CI, 1.60–1.80), prelabor CD (aOR, 1.73; 95% CI, 1.62–1.84), and indicated PTB (aOR, 3.90; 95% CI, 3.66–4.15). However, no association was found between maternal CH and spontaneous PTB (aOR, 1.07; 95% CI, 0.96–1.20). When we further explored the impact of CH on different categories of PTB, extreme, severe, and moderate PTB were also considerably higher among women with CH than normotensive women. Stillbirth and SGA were associated with CH (aOR, 1.65; 95% CI, 1.35–2.03; aOR, 3.55; 95% CI, 3.31–3.80, respectively). Women with CKD in pregnancy had higher odds of PE (aOR, 1.61; 95% CI, 1.51–1.73), in-labor CD (aOR, 1.36; 95% CI, 1.29–1.43), and prelabor CD (aOR, 1.60; 95% CI, 1.52–1.69) than normotensive women without CKD. Maternal CKD was associated with both spontaneous PTB (aOR, 1.24; 95% CI, 1.15–1.33) and indicated PTB (aOR, 2.05; 95% CI, 1.92–2.19). In addition, mothers with CKD had almost double the odds of extreme, severe, and moderate preterm delivery compared with normotensive women (Table 2).
Maternal CKD was also associated with higher odds of SGA (aOR, 1.29; 95% CI, 1.19-1.39). However, the association with stillbirth did not reach a significant level in the adjusted model (aOR, 1.16; 95% CI, 0.95-1.43).

Stronger associations were found in women with both conditions (Table 2). Women with both conditions (CH and CKD) had higher odds of SGA (aOR, 1.4; 95% CI, 1.3-1.5) and stillbirth (aOR, 1.2; 95% CI, 1.0-1.4) compared to normotensive women without CKD.

### Table 1

| Characteristic          | Normotensive (N=2,751,735) | CH (n=13,279) | CKD (n=22,397) | Women with CH and CKD (n=1079) |
|-------------------------|-----------------------------|---------------|----------------|--------------------------------|
| Maternal age, y         |                             |               |                |                                |
| <20                     | 70,097 (2.6)                | 60 (0.5)      | 586 (2.6)      | 24 (2.2)                       |
| 20-24                   | 523,437 (19)                | 1134 (8.5)    | 4106 (18)      | 149 (14)                       |
| 25-29                   | 954,962 (35)                | 3323 (25)     | 7173 (32)      | 277 (26)                       |
| 30-34                   | 807,727 (29)                | 4508 (34)     | 6651 (30)      | 318 (29)                       |
| 35-39                   | 334,592 (12)                | 3189 (24)     | 3213 (14)      | 254 (23.5)                     |
| ≥40                     | 60,920 (2.2)                | 1065 (8.0)    | 668 (3)        | 57 (5.3)                       |
| Mean (SD)               | 28.8 (5.2)                  | 31.8 (5.3)    | 29.2 (5.4)     | 30.7 (5.7)                     |
| Smoking                 |                             |               |                |                                |
| No                      | 2,185,536 (79)              | 11,225 (84)   | 16,779 (75)    | 876 (81)                       |
| 1-9 cigarettes/d        | 261,543 (9.5)               | 950 (7.2)     | 2851 (12.7)    | 114 (11)                       |
| ≥10 cigarettes/d        | 131,733 (4.8)               | 521 (3.9)     | 1636 (7.3)     | 41 (3.8)                       |
| Missing                 | 172,923 (6.3)               | 583 (4.4)     | 1131 (5.1)     | 48 (4.6)                       |
| BMI, kg/m²              |                             |               |                |                                |
| Underweight             | 78,868 (2.9)                | 137 (1.0)     | 703 (3.1)      | 26 (2.4)                       |
| Normal                  | 1,403,343 (51)              | 4380 (33)     | 11,322 (51)    | 466 (43)                       |
| Overweight              | 459,262 (17)                | 3210 (24)     | 4198 (19)      | 216 (20)                       |
| Obese                   | 182,752 (6.6)               | 2889 (22)     | 1919 (8.6)     | 166 (15)                       |
| Missing                 | 627,510 (23)                | 2663 (20)     | 4255 (19)      | 205 (19)                       |
| Parity                  |                             |               |                |                                |
| 0                       | 1,306,244 (47)              | 5429 (41)     | 9789 (44)      | 510 (47)                       |
| 1                       | 986,445 (36)                | 4836 (36)     | 7901 (35)      | 384 (36)                       |
| 2 or more               | 459,046 (17)                | 3014 (23)     | 4707 (21)      | 185 (17)                       |
| Country of origin       |                             |               |                |                                |
| Sweden                  | 2,267,401 (83)              | 11,412 (86)   | 18,401 (82)    | 890 (83)                       |
| Other Scandinavian      | 79,440 (2.9)                | 537 (4)       | 521 (2.3)      | 31 (2.9)                       |
| Elsewhere               | 392,907 (14)                | 1306 (9.8)    | 3405 (15)      | 154 (14)                       |
| Missing                 | 11,987 (0.4)                | 24 (0.2)      | 70 (0.3)       | 4 (0.4)                        |
| DM                      | 17,475 (0.64)               | 720 (5.5)     | 541 (2.4)      | 280 (26)                       |
| CVD                     | 3059 (0.11)                 | 98 (0.74)     | 71 (0.32)      | 22 (2.04)                      |
| Asthma                  | 124,003 (4.5)               | 1007 (7.6)    | 1853 (8.3)     | 186 (17)                       |

Values are expressed as number (percentage) unless indicated otherwise.

BMI, body mass index; CH, chronic hypertension; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; SD, standard deviation.

*Normotensive women refer to women without hypertension and chronic kidney disease.*

1 Underweight (BMI, <18.5 kg/m²), normal (BMI, 18.5 to <25 kg/m²), overweight (BMI, 25 to <30 kg/m²), and obese (BMI, ≥30 kg/m²).

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CKD) had approximately a 4-fold increased odds of PE (aOR, 4.16; 95% CI, 3.40–5.09) compared with normotensive women without CKD. Similarly, women with both conditions had higher odds of in-labor and prelabor CD (aOR, 1.86; 95% CI, 1.49–2.32; aOR, 2.68; 95% CI, 2.18–3.28, respectively), medically indicated PTB (aOR, 9.09; 95% CI, 7.61–10.7), and extreme PTB (<28 weeks) (aOR, 14.7; 95% CI, 10.1–21.3). The adjusted estimates for severe and moderate PTB were also significantly higher among women with both conditions than other groups.
### TABLE 3
The association between subtypes of chronic kidney disease and perinatal outcomes (singleton pregnancies in 1982–2012)

| Outcome Exposure | Preeclampsia | In-labor cesarean delivery | Prelabor cesarean delivery | Spontaneous preterm birth (<37 wk) |
|------------------|-------------|---------------------------|----------------------------|----------------------------------|
|                   | Cases, n (%) | Crude OR (95% CI) a       | Adjusted OR (95% CI) b    | Cases, n (%) | Crude OR (95% CI) a       | Adjusted OR (95% CI) c |
| Normotensive without CKD (n=2,751,735) | 75,931 (2.8) | Reference                 | Reference                   | 176,081 (7.9) | Reference                 | Reference |
| Tubulointerstitial (n=1784) | 73 (4.1) | 1.63 (1.27–2.10) | 1.55 (1.20–2.03) | 193 (13) | 1.23 (1.04–1.45) | 1.29 (1.09–1.53) |
| Glomerular (n=4367) | 247 (5.7) | 2.18 (1.89–2.52) | 2.13 (1.84–2.47) | 432 (13) | 1.48 (1.32–1.66) | 1.43 (1.27–1.61) |
| Diabetic nephropathy (n=266) | 52 (20) | 8.45 (6.12–11.7) | 2.17 (1.54–3.04) | 62 (57) | 15.4 (9.57–24.7) | 3.54 (2.06–6.09) |
| Renovascular disease (n=220) | 25 (11) | 4.33 (2.74–6.85) | 3.64 (2.18–6.09) | 27 (17) | 3.10 (2.08–4.64) | 2.73 (1.78–4.18) |
| CAKUT (n=534) | 58 (11) | 4.34 (3.29–5.72) | 3.98 (2.98–5.31) | 55 (16) | 1.99 (1.45–2.72) | 1.99 (1.44–2.75) |
| Other or unspecified CKD (n=6431) | 277 (4.3) | 1.59 (1.40–1.82) | 1.59 (1.39–1.81) | 540 (11) | 1.35 (1.23–1.49) | 1.40 (1.27–1.55) |
|                   |            |                          |                            |                   |                          | |
| Normotensive without CKD (n=2,231,697) | 176,081 (7.9) | Reference                 | Reference                   | 149,199 (6.8) | Reference                 | Reference |
| Tubulointerstitial (n=1435) | 193 (13) | 1.23 (1.04–1.45) | 1.29 (1.09–1.53) | 130 (9.5) | 1.44 (1.18–1.76) | 1.15 (0.94–1.42) |
| Glomerular (n=3349) | 432 (13) | 1.48 (1.32–1.66) | 1.43 (1.27–1.61) | 439 (13) | 2.07 (1.84–2.33) | 1.68 (1.48–1.90) |
| Diabetic nephropathy (n=109) | 62 (57) | 15.4 (9.57–24.7) | 3.54 (2.06–6.09) | 62 (57) | 15.4 (9.57–24.7) | 3.54 (2.06–6.09) |
| Renovascular (n=161) | 27 (17) | 3.10 (2.08–4.64) | 2.73 (1.78–4.18) | 27 (17) | 3.10 (2.08–4.64) | 2.73 (1.78–4.18) |
| CAKUT (n=355) | 55 (16) | 1.99 (1.45–2.72) | 1.99 (1.44–2.75) | 55 (16) | 1.99 (1.45–2.72) | 1.99 (1.44–2.75) |
| Other or unspecified CKD (n=5045) | 540 (11) | 1.35 (1.23–1.49) | 1.40 (1.27–1.55) | 540 (11) | 1.35 (1.23–1.49) | 1.40 (1.27–1.55) |
|                   |            |                          |                            |                   |                          | |
| Normotensive without CKD (n=2,204,815) | 149,199 (6.8) | Reference                 | Reference                   | 149,199 (6.8) | Reference                 | Reference |
| Tubulointerstitial (n=1372) | 130 (9.5) | 1.44 (1.18–1.76) | 1.15 (0.94–1.42) | 130 (9.5) | 1.44 (1.18–1.76) | 1.15 (0.94–1.42) |
| Glomerular (n=3356) | 439 (13) | 2.07 (1.84–2.33) | 1.68 (1.48–1.90) | 439 (13) | 2.07 (1.84–2.33) | 1.68 (1.48–1.90) |
| Diabetic nephropathy (n=152) | 105 (69) | 30.8 (20.6–45.8) | 7.50 (4.74–11.9) | 105 (69) | 30.8 (20.6–45.8) | 7.50 (4.74–11.9) |
| Renovascular (n=169) | 35 (21) | 3.60 (2.45–5.30) | 4.02 (2.66–6.08) | 35 (21) | 3.60 (2.45–5.30) | 4.02 (2.66–6.08) |
| CAKUT (n=386) | 86 (22) | 3.95 (3.05–5.11) | 4.19 (3.19–5.49) | 86 (22) | 3.95 (3.05–5.11) | 4.19 (3.19–5.49) |
| Other or unspecified CKD (n=5058) | 553 (11) | 1.69 (1.52–1.88) | 1.55 (1.39–1.72) | 553 (11) | 1.69 (1.52–1.88) | 1.55 (1.39–1.72) |
|                   |            |                          |                            |                   |                          | |
| Normotensive without CKD (n=2,678,800) | 67,792 (2.5) | Reference                 | Reference                   | 67,792 (2.5) | Reference                 | Reference |
| Tubulointerstitial (n=1705) | 55 (3.2) | 0.89 (0.67–1.18) | 0.82 (0.62–1.09) | 55 (3.2) | 0.89 (0.67–1.18) | 0.82 (0.62–1.09) |
| Glomerular (n=4063) | 196 (4.8) | 1.71 (1.46–2.01) | 1.60 (1.37–1.89) | 196 (4.8) | 1.71 (1.46–2.01) | 1.60 (1.37–1.89) |
| Diabetic nephropathy (n=142) | 8 (5.6) | 2.22 (1.08–4.57) | 0.90 (0.43–1.89) | 8 (5.6) | 2.22 (1.08–4.57) | 0.90 (0.43–1.89) |
| Renovascular disease (n=165) | 10 (6.1) | 3.25 (1.69–6.23) | 3.01 (1.57–5.76) | 10 (6.1) | 3.25 (1.69–6.23) | 3.01 (1.57–5.76) |
| CAKUT (n=483) | 19 (3.9) | 1.45 (0.90–2.36) | 1.33 (0.82–2.16) | 19 (3.9) | 1.45 (0.90–2.36) | 1.33 (0.82–2.16) |
| Other or unspecified CKD (n=6024) | 174 (2.9) | 1.11 (0.95–1.30) | 1.08 (0.93–1.27) | 174 (2.9) | 1.11 (0.95–1.30) | 1.08 (0.93–1.27) |

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Mothers with both conditions were more likely to have SGA babies (aOR, 4.52; 95% CI, 3.68–5.57). Nevertheless, no effect was found for both conditions on spontaneous PTB and stillbirth. In addition, the strength of associations between both conditions and adverse pregnancy outcomes was attenuated after adjusting for diabetes mellitus, which might reflect the high percentage of diabetes among these women (26%).

**Adverse maternal and perinatal outcomes among women with subtypes of chronic kidney disease**

The incidence and the associations between CKD subtypes and adverse perinatal outcomes are presented in Table 3. All CKD subtypes were associated with higher odds of PE, in-labor CD, and medically indicated PTB. Women with diabetic nephropathy had noticeable higher odds for adverse outcomes. However, after adjusting for potential confounders, women with diabetic nephropathy had the strongest

### Table 3

The association between subtypes of chronic kidney disease and perinatal outcomes (singleton pregnancies in 1982–2012) (continued)

| Medically indicated preterm birth | Cases, n (%) | Crude OR (95% CI) \(^a\) | Adjusted OR (95% CI) \(^c\) |
|----------------------------------|--------------|---------------------------|-----------------------------|
| Normotensive without CKD (n=2,683,943) | 72,935 (2.7) | Reference | Reference |
| Tubulointerstitial (n=1,729) | 79 (4.6) | 3.11 (2.43–3.97) | 2.74 (2.15–3.50) |
| Glomerular (n=4,171) | 304 (7.3) | 3.62 (3.17–4.12) | 3.10 (2.71–3.53) |
| Diabetic nephropathy (n=258) | 124 (48) | 32.9 (25.1–43.1) | 6.52 (4.94–8.6) |
| Renovascular disease (n=210) | 55 (26) | 9.94 (7.05–14.0) | 8.09 (5.73–11.4) |
| CAKUT (n=515) | 51 (10) | 4.11 (3.02–5.60) | 3.73 (2.72–5.11) |
| Other or unspecified CKD (n=6,257) | 407 (6.5) | 2.57 (2.29–2.87) | 2.38 (2.13–2.67) |

| Stillbirth | Cases, n (%) | Crude OR (95% CI) \(^a\) | Adjusted OR (95% CI) \(^c\) |
|------------|--------------|---------------------------|-----------------------------|
| Normotensive without CKD (n=2,751,735) | 9135 (0.33) | Reference | Reference |
| Tubulointerstitial (n=1,784) | 8 (0.45) | 1.36 (0.68–2.71) | 1.28 (0.64–2.56) |
| Glomerular (n=4,367) | 19 (0.44) | 1.31 (0.82–2.11) | 1.12 (0.70–1.79) |
| Diabetic nephropathy (n=266) | 5 (1.88) | 5.75 (2.40–13.8) | 1.55 (0.64–3.76) |
| Renovascular disease (n=220) | 2 (0.91) | — | — |
| CAKUT (n=534) | 5 (0.94) | 2.84 (1.18–6.82) | 2.73 (1.13–6.59) |
| Other or unspecified CKD (n=6,431) | 18 (0.28) | 0.84 (0.53–1.34) | 0.80 (0.50–1.26) |

| Small for gestational age | Cases, n (%) | Crude OR (95% CI) \(^a\) | Adjusted OR (95% CI) \(^c\) |
|--------------------------|--------------|---------------------------|-----------------------------|
| Normotensive without CKD (n=2,751,735) | 70,202 (2.6) | Reference | Reference |
| Tubulointerstitial (n=1,784) | 54 (3.0) | 1.43 (1.09–1.87) | 1.25 (0.94–1.65) |
| Glomerular (n=4,367) | 184 (4.2) | 1.81 (1.54–2.12) | 1.54 (1.31–1.81) |
| Diabetic nephropathy (n=266) | 26 (9.8) | 4.01 (2.65–6.08) | 4.50 (2.92–6.94) |
| Renovascular disease (n=220) | 24 (11) | 4.28 (2.77–6.60) | 3.28 (2.06–5.20) |
| CAKUT (n=534) | 35 (6.6) | 2.73 (1.89–3.95) | 2.45 (1.66–3.60) |
| Other or unspecified CKD (n=6,431) | 223 (3.5) | 1.39 (1.20–1.60) | 1.35 (1.17–1.56) |

BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; CI, confidence interval; CKD, chronic kidney disease; ID, identity document; OR, odds ratio.

\(^a\) All crude estimates cluster on mothers’ ID and adjusted for year of birth; \(^b\) Adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), birth year, and child’s sex; \(^c\) Adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), and birth year.

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associations for in-labor CD (aOR, 3.54; 95% CI, 2.06–6.09), prelabor CD (aOR, 7.50; 95% CI, 4.74–11.9), and SGA (aOR, 4.50; 95% CI, 2.92–6.94). Although women with congenital kidney disease had the most pronounced increase odds of PE (aOR, 3.98; 95% CI, 2.98–5.31) and stillbirth (aOR, 2.73; 95% CI, 1.13–6.59). The associations of PTB were stronger in women with renovascular disease (spontaneous PTB, aOR, 3.01; 95% CI, 1.57–5.76; indicated PTB, aOR, 8.09; 95% CI, 5.73–11.4).

**Adverse perinatal outcomes among women with chronic hypertension, chronic kidney disease, or both conditions over the last 3 decades**

When we assessed the association among maternal CH, CKD, and a combination of both conditions over a 5-year period, there were no clear patterns of these associations over time (Figure, Supplemental Table 2). However, a noticeable reduction in the odds of prelabor CD and PTB was observed in the last 5 years (2007–2012) in women with CH, CKD, and both conditions. The results of the subgroup and sensitivity analyses are presented in the Supplemental Material (page 3 and Supplemental Tables 3–6).

**Discussion**

**Principal findings and interpretation**

This large cohort study demonstrated that maternal and fetal complications remain high in women with CKD, CH, or both conditions, and these higher risks persisted independently of parity, maternal age, and BMI. Multiparous women with these conditions had worse outcomes than nulliparous women. This study adds significantly to the literature because we used a large cohort, which allowed us to undertake further analyses and investigate the effect of different subtypes of CKD. Our findings suggest that the risk of adverse pregnancy outcomes was higher in women with diabetic nephropathy, renovascular disease, and congenital kidney disease than other CKD subtypes.

**Compared with previous studies**

Our findings on the association between maternal CH and adverse perinatal outcomes are consistent with previous population-based studies on PE, stillbirth, medically indicated PTB, and SGA. However, 2 studies reported adjusted results for prelabor CD, and a recent United Kingdom cohort study suggested an association, whereas a Netherlands study did not find an association between CH and prelabor CD. Interestingly, we found a lack of relationship between CH and spontaneous PTB, and this was consistent with the findings from 2 previous cohort studies. Few previous reports evaluated the effects of maternal age and other characteristics on the associations between CH and adverse pregnancy outcomes. A Canadian cohort study including 134,088 women reported a higher prevalence of CD (without specifying its type) among older women with CH, which was similar to our results for prelabor and in-labor CD.

We have conducted the largest study of pregnancy outcomes in women with CKD from the last 3 decades. In consistent with our findings, previous studies have reported an association between CKD and adverse pregnancy outcomes. Moreover, in our study, the adjusted odds of PE in patients with CKD was 1.61, which is lower than the reported pooled estimate in a meta-analysis of 9 studies on PE (OR, 10.36). However, only 3 of the 9 studies adjusted for confounding variables, whereas 6 of these studies included patients with diabetic nephropathy.
results of PE in women with diabetic nephropathy were similar with an OR of 8.45, but that decreased to 2.17 after adjustment for confounders. Although pregnancy complications were higher in women with CKD, the live birth rate was high because we found a nonsignificant relationship between maternal CKD and stillbirth. A previous study in the United States including 502,186 singleton births reported a higher rate of stillbirth in women with CKD (6.4%) vs those without (0.3%), but they did not report an adjusted estimate. The result from a meta-analysis suggested an association between pregnancy failure and maternal CKD; however, the outcome was a composite of stillbirth, fetal death, and neonatal death together. None of the previous studies on CKD have evaluated the effect of maternal sociodemographic factors on adverse perinatal outcomes.

There is also limited research on the risk of adverse pregnancy outcomes among women with specific kidney disease. Our study demonstrated adverse pregnancy outcomes in women with congenital kidney disease. A previous case series of 37 pregnancies in 20 patients, evaluating the effect of congenital urinary tract abnormality and reconstruction on pregnancy, reported a higher rate of PE and CD than general obstetrical population, whereas no adverse outcomes in infants were reported. A recent retrospective cohort study by Li et al. (2018), in pregnancies with chronic glomerulonephritis, reported higher rates of premature delivery, low birthweights, and intrauterine growth restriction than pregnancy without CKD. Although our results in women with glomerular CKD are similar to this study, adjusted estimates were not reported and it used data from a single center with a small sample size (N=114).

Clinical and research implications

Women with CH, CKD, or both conditions should be monitored carefully during pregnancy and delivery, specifically multiparous women and women with diabetic nephropathy, congenital kidney disease, or renovascular disease. Multidisciplinary antenatal management, including nephrologists and obstetricians, should be provided with intensive clinical follow-up to support women with CKD during pregnancy and importantly in the postnatal period. Although the Kidney Disease Outcomes Quality Initiative and the National Institute for Health and Care Excellence (NICE) have not provided specific guidance on the management of kidney disease during pregnancy, the available guidance recommended that women with CKD should be offered preconception counseling by a multidisciplinary team and blood pressure should be optimized before pregnancy. In addition, a blood pressure goal of <140/90 mm Hg has been recommended with close surveillance during pregnancy for women with CKD. Similarly, the available guidance from NICE and the American College of Obstetricians and Gynecologists recommend that women with CH should be assessed before conception and monitored closely for the potential development of adverse complications during pregnancy.

Future research should consider severity of maternal disease (CH and CKD) when assessing the association with adverse perinatal outcomes. Moreover, more population-based studies needed to evaluate the impact of specific kidney disease on adverse perinatal outcomes and therapeutic interventions to improve maternal and fetal outcomes.

Strengths and limitations

Our study has several strengths. First, unlike most of the previous studies focusing on the effects of CH or CKD, we performed 3 groups based on the existing of each chronic condition alone or a combination of both. Second, we used data from MBR which contains data on approximately all births in Sweden, and that increases the generalizability of our findings and eliminate selection bias. Third, data were prospectively collected from MBR on maternal and fetal characteristics. Fourth, detailed information on maternal characteristics and a wide range of well-defined adverse pregnancy outcomes enabled us to control for risk factors associated with adverse perinatal outcome. Fifth, we used data over 30 years, which allowed us to assess the associations over time. Sixth, the large number of participants allowed us to stratify the associations by maternal characteristics.

This study has some limitations need to be addressed. The observational nature of our study introduces a potential issue of residual confounders. However, we adjusted for a vast number of important confounders. We also conducted stratified analyses according to maternal characteristics (maternal age, BMI, and parity) to further understand their effects on the associations. Other limitations refer to missing values for smoking during pregnancy and BMI of the study cohort. However, as mentioned in the Materials and Methods section, an indicator category was created for missing values to adjust for this issue in the analysis phase. In this study, we did not evaluate the effect of disease severity on adverse outcome, but these is beyond the scope of this investigation.

Conclusion

Our findings showed that adverse pregnancy outcomes increase in women with CH, CKD, or both conditions which were independent of maternal age, BMI, and parity. Multiparous women with these conditions had worse adverse perinatal outcomes. Women with these conditions should be monitored carefully during pregnancy and delivery. Larger prospective studies are needed to assess the effect of disease severity and specific kidney disease on adverse pregnancy outcomes.

References

1. Hussain A, Karovitch A, Carson MP. Blood pressure goals and treatment in pregnant patients with chronic kidney disease. Adv Chronic Kidney Dis 2015;22:165–9.
2. Nevis IF, Reitsma A, Dominic A, et al. Pregnancy outcomes in women with chronic kidney disease.
disease: a systematic review. Clin J Am Soc Nephrol 2011;6:2587–98.
3. Zhang JJ, Ma XK, Hao L, Liu LJ, Lv JC, Zhang H. A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD outcomes in pregnancy. Clin J Am Soc Nephrol 2015;10:1964–76.
4. Bramham K, Polli-de-Figueiredo CE, Seed PT, et al. Association of proteinuria threshold in pre-eclampsia with maternal and perinatal outcomes: a nested case control c...of high risk women. PLoS One 2013;8:e76083.
5. Piccoli GB, Cabiddu G, Attini R, et al. Risk of adverse pregnancy outcomes in women with CKD. J Am Soc Nephrol 2015;26:2011–22.
6. Farwell J, Emerson J, Wyatt S, Rueda J, Cheng Y, Caughley A. Outcomes of pregnancies complicated by chronic kidney disease. Am J Obstet Gynecol 2013;208:S153–4.
7. Fink JC, Schwartz SM, Benedetti TJ, Stehman-Breen CO. Increased risk of adverse maternal and infant outcomes among women with renal disease. Paediatr Perinat Epidemiol 1998;12:277–87.
8. Jensen DM, Damm P, Ovesen P, et al. Microalbuminuria, preclampsia, and preterm delivery in pregnant women with type 1 diabetes: results from a nationwide Danish study. Diabetes Care 2010;33:90–4.
9. Ekborg P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Melvig J, Mathiesen ER. Pregnancy outcome in type 1 diabetic women with microalbuminuria. Diabetes Care 2001;24:1739–44.
10. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol 2017;50:228–35.
11. Ananth CV, Dzyj CM, Yadava S, Schwebel M, Tita ATN, Joseph KS. Changes in the prevalence of chronic hypertension in pregnancy, United States, 1970 to 2010. Hypertension 2019;74:1089–95.
12. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ 2014;348:g2300.
13. Lydiak C, Beever DG, Beever MG, Lip GY. Obstetric and neonatal outcome following chronic hypertension in pregnancy among different ethnic groups. JQM 1998;91:837–44.
14. Yanit KE, Snowden JM, Cheng YW, Caughley AB. The impact of chronic hypertension and pregestational diabetes on pregnancy outcomes. Am J Obstet Gynecol 2012;207:333.e1–6.
15. Tuuli MG, Rampsad R, Stillman D, Macones G, Odibo AO. Perinatal outcomes in women with preeclampsia and superimposed preeclampsia: do they differ? Am J Obstet Gynecol 2011;204:508.e1–7.
16. Yang Y, He Y, Li Q, et al. Preconception blood pressure and risk of preterm birth: a large historical cohort study in a Chinese rural population. Fertil Steril 2015;104:124–30.
17. Premkumar A, Henry DE, Moghadam M, Nakagawa S, Norton ME. The interaction between maternal race/ethnicity and chronic hypertension on preterm birth. Am J Obstet Gynecol 2016;215:787.e1–8.
18. Samadi AR, Mayberry RM. Maternal hypertension and spontaneous preterm births among black women. Obstet Gynecol 1998;91:909–904.
19. Kramer MS, Demissie K, Yang H, Platt RW, Sauvé R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA 2000;284:843–9.
20. Bernstein IM, Horbar JD, Badger GJ, Ohtsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. Am J Obstet Gynecol 2000;182:198–206.
21. Lees C, Marlow N, Arabin B, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013;42:400–8.
22. Nanningius S, Ericson A, Gunnarskog J, Källén B. A quality study of a medical birth registry. Scand J Soc Med 1990;18:143–5.
23. Corsello G, Piro E. The world of twins: an update. J Matern Fetal Neonatal Med 2010;23(Suppl3):59–62.
24. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekborg A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;24:659–67.
25. Goldenberg RL, Culhane JF, Iams JD, and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA 2000;284:143–8.
26. Pasternak B, Wintzell V, Furu K, Engeland A, Novius M, Stephansson OJ. Oral furocanazole in pregnancy and risk of stillbirth and neonatal death. JAMA 2018;319:2333–5.
27. Broekhuizen K, Ravelli AC, Langenveld J, et al. Maternal and neonatal outcomes of pregnancy in women with chronic hypertension: a retrospective analysis of a national registry. Acta Obstet Gynecol Scand 2015;94:1337–45.
28. You SH, Cheng PJ, Chung TT, Kuo CF, Wu HM, Chu PH. Population-based trends and risk factors of early- and late-onset preeclampsia in Taiwan 2001-2014. BMC Pregnancy Childbirth 2018;18:199.
29. Catov JM, Ness RB, Kip KE, Olsen J. Risk of early or severe pre-eclampsia related to preexisting conditions. Int J Epidemiol 2007;36:412–9.
30. Ahmad AS, Samuelson SO. Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2 121 371 pregnancies. BJOG 2012;119:1521–8.

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**Supplemental Material**

**Supplemental Methods**

Potential confounders that we adjusted for included maternal demographic characteristics and comorbidities. Information about maternal age was categorized into 5-year categories (<20, 20–24, 25–29, 30–34, 35–39, and 40 years or older), smoking habits recorded during the first antenatal visit (non-smokers, moderate smokers [1–9 cigarettes/day], and heavy smokers [≥10 cigarettes/day]). We calculated maternal body mass index (BMI) using the women’s height and prepregnancy weight (kg/m²), which was categorized into the following subgroups: underweight (BMI, <18.5 kg/m²), normal (BMI, 18.5–25 kg/m²), overweight (BMI, 25–30 kg/m²), and obese (BMI, ≥30 kg/m²). Parity was categorized as follows: “parity 0,” no previous birth; “parity 1,” 1 previous birth; and “parity 2,” if a woman had 2 or more previous births. Country of origin was categorized as Sweden, other Scandinavian countries, or elsewhere. Other comorbidities included asthma, diabetes mellitus (DM), and cardiovascular disease (CVD). Data on these variables were collected from the Swedish Medical Birth Register, in addition to National Patient Register for comorbidities variables. Maternal highest educational level was obtained from the Swedish Education Register and was based on the mothers’ highest level of education.

When we investigated the risk of preeclampsia, we adjusted for child’s sex because previous studies suggested an association between fetal sex and preeclampsia. We conducted subgroup analyses to examine the effect of parity (primigravida, multigravida), maternal age (<35 years or ≥35 years), and BMI categories on adverse perinatal outcomes. In all analyses, we accounted for the potential clustering within family. In addition, sensitivity analyses were performed excluding women with other comorbidities including DM, CVD, and asthma.

**Supplemental Results**

**The sensitivity analyses according to maternal characteristics**

Stratified results by parity demonstrated that multiparous women with chronic hypertension (CH), chronic kidney disease (CKD), or both conditions had worse outcomes than nulliparous women (Supplemental Table 3). The adjusted estimates for preeclampsia, in multiparous women, were remarkably higher in women with CH (adjusted odds ratio [aOR], 6.02; 95% confidence interval [CI], 5.59–6.49), CKD (aOR, 2.09; 95% CI, 1.88–2.32), and both conditions (aOR, 7.22; 95% CI, 5.55–9.40).

The subgroup analyses by maternal age suggested that younger women (<35 years old) with CH, CKD, or both conditions were more likely to deliver by prelabor cesarean delivery (CD) and to have spontaneous preterm birth (Supplemental Table 4). In contrast, older women (≥35 years old) with CH or CKD had higher odds of medically indicated preterm birth, stillbirth, and small for gestational age. Although the incidence of adverse outcomes increased with increasing BMI, the adjusted estimates of preeclampsia, in-labor CD, prelabor CD, preterm birth, and small for gestational age decreased gradually with increasing BMI, in women with CH (Supplemental Table 5).

The results of sensitivity analysis (excluding women with other comorbidities) are shown in Supplemental Table 6. The associations for women with CH or CKD did not materially change, but it seems that most of the confounding effects were related to the confounders we excluded in this analysis (DM, CVD, and asthma), because some adjusted estimates become larger in women with both conditions than normotensive women without CKD. For example, the aOR for spontaneous preterm birth became significant (aOR, 1.70; 95% CI, 1.09–2.67). In addition, the aORs for preeclampsia (aOR, 7.37; 95% CI, 5.93–9.14) and small for gestational age (aOR, 5.38; 95% CI, 4.27–6.80) were stronger than crude estimates in women with both conditions. However, that did not change our conclusion.

**Supplemental References**

1. Zheng Q, Deng Y, Zhong S, Shi Y. Human chorionic gonadotropin, fetal sex and risk of hypertensive disorders of pregnancy: a nested case-control study. Pregnancy Hypertens 2016;6:17–21.
2. Shiozaki A, Matsuda Y, Satoh S, Saito S. Impact of fetal sex in pregnancy-induced hypertension and preeclampsia in Japan. J Reprod Immunol 2011;89:133–9.
SUPPLEMENTAL FIGURE 1
Flowchart of the study population

Births between 1973 and 2012
N= 4,073,947

1,208,556 births excluded as their mothers had their 1st pregnancy before 1982

76,817 multiple births excluded

Births between 1982 and 2012
N= 2,788,574

1,208,556 births excluded as their mothers had their 1st pregnancy before 1982

Number of excluded women=627,389

Number of excluded women=13,674

Number of women=1,420,846

Number of women=1,420,846

76,817 multiple births excluded

84 duplicates dropped (Based on mothers’ id and date of birth)

Births in the final cohort between 1st January1982 and 31st December 2012
N= 2,788,490

Number of women=1,420,846

SUPPLEMENTAL FIGURE 2
Trends in the prevalence of maternal chronic disease (CH, CKD or both) over the last 3 decades

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### SUPPLEMENTAL TABLE 1

**ICD**

| Disease                                      | ICD-8 codes (1973—1986) | ICD-9 codes (1987—1996) | ICD-10 codes (1997—2013) |
|----------------------------------------------|-------------------------|-------------------------|---------------------------|
| Preeclampsia or eclampsia                   | 637.00, 637.03, 637.04, 637.09, 637.10, 637.19, 637.90, 637.99 | 642E, 642F, 642G, 642H | 0110, 0119, 0140, 0141, 0141A, 014B, 0141C, 0141X, 0142, 0149, 0150, 0151, 0152, 0159 |
| Subtypes of CKD                             |                         |                         |                           |
| Tubulointerstitial CKD                      | —                       | —                       | N11-N12, N15-N16          |
| Glomerular/proteinuric CKD                  | —                       | 581—583                 | N01-N06, N08              |
| Diabetic nephropathy                        | 250.04                  | 250D                    | E10.2, E10.2A, E10.2B, E10.2C, E10.2W, E10.2X, E11.2A, E11.2B, E11.2C, E11.2W, E11.2X, E13.2, E14.2 |
| Renovascular disease                        | 403—404                 | 403—404                 | I12.0-I13.9, I15.0, I15.1 |
| Congenital anomalies of the kidney and urinary tract | 753.00—753.99          | 753                     | Q60.0—Q64.9, Q27.1, Q27.2 |
| Other or unspecified CKD                    | 581.00—584.99           | 585—588, V45B, V56A, V56W | N130-N139, N18-N19, Z49.0-Z49.2, Z99.2, |

CKD, chronic kidney disease; ICD, International Classification of Diseases; ICD-8, International Classification of Diseases, Eighth Revision; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

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### SUPPLEMENTAL TABLE 2

**Adjusted estimates for the association between maternal chronic diseases and adverse pregnancy outcomes over time from 1982 to 2012**

| Outcome                              | Normotensive women Cases, n (%) OR (95% CI) | Pregnancies with CH Cases, n (%) OR (95% CI) | Pregnancies with CKD Cases, n (%) OR (95% CI) | Pregnancies with CH and CKD Cases, n (%) OR (95% CI) |
|--------------------------------------|--------------------------------------------|---------------------------------------------|-----------------------------------------------|---------------------------------------------------|
| Preeclampsia‡                        |                                            |                                             |                                               |                                                   |
| 1982—1986                           | 14,181 (5.3) Reference 133 (27) 4.65 (3.73–5.80) 111 (10) 1.87 (1.52–2.29) 10 (14) 2.98 (1.49–5.93) |
| 1987—1991                           | 13,323 (1.9) Reference 277 (16) 8.30 (7.18–9.59) 73 (2.9) 1.44 (1.13–1.83) 8 (6.5) 2.60 (1.22–5.51) |
| 1992—1996                           | 10,210 (2.1) Reference 261 (9.4) 3.81 (3.31–4.39) 131 (2.9) 1.43 (1.19–1.71) 17 (10) 3.41 (1.90–6.14) |
| 1997—2001                           | 12,260 (3.0) Reference 213 (17) 4.84 (4.11–5.70) 131 (4.3) 1.48 (1.23–1.77) 16 (19) 5.04 (2.60–9.79) |
| 2002—2006                           | 12,914 (2.7) Reference 447 (16) 5.01 (4.46–5.63) 233 (4.9) 1.82 (1.58–2.09) 39 (20) 6.19 (3.97–9.65) |
| 2007—2012                           | 17,134 (2.8) Reference 607 (14) 4.12 (3.73–4.56) 300 (4.6) 1.69 (1.50–1.92) 85 (19) 3.95 (2.90–5.38) |
| In-labor cesarean delivery§          |                                            |                                             |                                               |                                                   |
| 1982—1986                           | 14,419 (6.4) Reference 72 (19) 2.43 (1.85–3.19) 101 (12) 1.89 (1.52–2.37) 8 (14) 2.41 (1.09–5.32) |
| 1987—1991                           | 17,553 (4.3) Reference 157 (12) 2.54 (2.12–3.03) 126 (6.3) 1.43 (1.18–1.73) 6 (7.8) 1.41 (0.62–3.19) |
| 1992—1996                           | 20,134 (4.9) Reference 93 (4.7) 0.79 (0.64–0.98) 193 (5.6) 1.08 (0.94–1.26) 11 (12) 1.99 (1.03–3.82) |
| 1997—2001                           | 24,683 (7.7) Reference 129 (15) 1.67 (1.37–2.04) 224 (9.8) 1.30 (1.13–1.50) 12 (25) 3.54 (1.69–7.41) |
| 2002—2006                           | 41,111 (11) Reference 481 (24) 1.85 (1.65–2.08) 508 (15) 1.38 (1.24–1.52) 37 (29) 2.25 (1.44–3.52) |
| 2007—2012                           | 58,181 (12) Reference 774 (25) 1.75 (1.59–1.92) 767 (16) 1.43 (1.31–1.56) 105 (32) 1.58 (1.15–2.16) |

‡ Al Khalaf et al. The impact of chronic kidney disease and chronic hypertension on adverse pregnancy outcomes. Am J Obstet Gynecol 2021.
### SUPPLEMENTAL TABLE 2
#### Adjusted estimates for the association between maternal chronic diseases and adverse pregnancy outcomes overt time from 1982 to 2012 (continued)

| Outcome                    | Normotensive women | Pregnancies with CH | Pregnancies with CKD | Pregnancies with CH and CKD |
|----------------------------|--------------------|---------------------|----------------------|-----------------------------|
|                             | Cases, n (%) OR (95% CI) | Cases, n (%) OR (95% CI) | Cases, n (%) OR (95% CI) | Cases, n (%) OR (95% CI) |
| Prelabor cesarean delivery<sup>4</sup> |                    |                     |                      |                             |
| 1982—1986 9962 (4.5) Reference | 45 (13) 1.84 (1.30—2.61) | 83 (9.9) 2.11 (1.65—2.71) | 8 (14) 3.45 (1.62—7.53) |
| 1987—1991 17,602 (4.3) Reference | 169 (13) 2.42 (2.03—2.88) | 170 (8.4) 1.86 (1.58—2.20) | 25 (26) 5.39 (3.29—8.81) |
| 1992—1996 22,905 (5.6) Reference | 349 (16) 2.25 (1.99—2.54) | 346 (9.6) 1.67 (1.49—1.88) | 56 (41) 7.40 (5.09—10.8) |
| 1997—2001 24,019 (7.5) Reference | 193 (21) 2.22 (1.88—2.63) | 272 (12) 1.51 (1.31—1.73) | 24 (40) 4.97 (2.86—8.64) |
| 2002—2006 32,354 (9.0) Reference | 317 (18) 1.49 (1.31—1.70) | 486 (14) 1.59 (1.43—1.76) | 37 (29) 2.82 (1.83—4.33) |
| 2007—2012 42,357 (8.8) Reference | 486 (17) 1.37 (1.23—1.53) | 621 (13) 1.50 (1.37—1.65) | 63 (22) 1.28 (0.92—1.79) |
| Preterm birth (<37 wk of gestation)<sup>5</sup> |                    |                     |                      |                             |
| 1982—1986 16,497 (6.1) Reference | 96 (19) 3.07 (2.43—3.89) | 131 (12) 1.81 (1.50—2.19) | 20 (28) 5.18 (3.09—8.67) |
| 1987—1991 25,359 (5.3) Reference | 237 (14) 2.65 (2.29—3.03) | 250 (10) 1.77 (1.55—2.03) | 37 (30) 5.93 (4.00—8.79) |
| 1992—1996 24,450 (4.9) Reference | 329 (12) 2.36 (2.10—2.67) | 334 (12) 1.43 (1.27—1.61) | 58 (36) 7.75 (5.48—11.0) |
| 1997—2001 20,668 (5.0) Reference | 192 (15) 2.96 (2.51—3.49) | 274 (8.0) 1.75 (1.54—1.99) | 29 (35) 7.51 (4.56—12.3) |
| 2002—2006 23,414 (5.0) Reference | 349 (13) 2.34 (2.08—2.64) | 399 (8.4) 1.67 (1.49—1.86) | 57 (29) 5.38 (3.76—7.71) |
| 2007—2012 30,486 (4.9) Reference | 528 (12) 2.31 (2.09—2.55) | 507 (7.8) 1.54 (1.40—1.70) | 108 (25) 3.22 (2.48—4.18) |
| Stillbirth<sup>6</sup> |                    |                     |                      |                             |
| 1982—1986 1007 (0.37) Reference | 7 (1.4) 3.03 (1.40—6.57) | 3 (0.27) — | 1 (1.4) — |
| 1987—1991 1557 (0.33) Reference | 10 (0.58) 1.49 (0.79—2.81) | 11 (0.44) 1.15 (0.63—2.08) | 0 — |
| 1992—1996 1498 (0.30) Reference | 20 (0.72) 1.86 (1.19—2.91) | 17 (0.38) 1.13 (0.70—1.84) | 0 — |
| 1997—2001 1480 (0.36) Reference | 10 (0.79) 1.65 (0.88—3.10) | 19 (0.62) 1.57 (0.99—2.47) | 1 (1.2) — |
| 2002—2006 1425 (0.30) Reference | 23 (0.83) 2.05 (1.34—3.14) | 15 (0.31) 0.97 (0.58—1.61) | 4 (2.0) — |
| 2007—2012 2168 (0.35) Reference | 28 (0.66) 1.31 (0.89—1.94) | 29 (0.45) 1.18 (0.81—1.72) | 1 (0.23) — |
| Small for gestational age<sup>7</sup> |                    |                     |                      |                             |
| 1982—1986 9656 (3.6) Reference | 75 (15) 4.59 (3.53—5.96) | 65 (5.8) 1.53 (1.17—2.01) | 5 (6.9) 1.87 (0.73—4.75) |
| 1987—1991 14,014 (2.9) Reference | 220 (13) 4.99 (4.30—5.80) | 118 (4.8) 1.45 (1.20—1.76) | 11 (8.9) 2.59 (1.35—4.96) |
| 1992—1996 12,356 (2.5) Reference | 185 (6.6) 2.96 (2.53—3.46) | 136 (3.0) 1.09 (0.91—1.31) | 24 (15) 6.51 (4.13—10.2) |
| 1997—2001 9614 (2.3) Reference | 107 (8.5) 4.13 (3.36—5.08) | 108 (3.6) 1.44 (1.18—1.75) | 6 (7.2) 3.57 (1.54—8.30) |
| 2002—2006 10,375 (2.2) Reference | 198 (7.2) 3.58 (3.07—4.18) | 139 (2.9) 1.25 (1.05—1.48) | 27 (14) 7.59 (4.87—11.8) |
| 2007—2012 14,187 (2.3) Reference | 262 (6.2) 2.93 (2.57—3.34) | 189 (2.9) 1.21 (1.04—1.41) | 38 (8.7) 4.70 (3.31—6.67) |

BMI, body mass index; CH, chronic hypertension; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio.

<sup>4</sup> Adjusted for maternal age, educational level, smoking, BMI, parity, country of origin, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), and child’s sex; <sup>5</sup> Adjusted for maternal age, educational level, smoking, BMI, parity, country of origin, and other comorbidities (diabetes mellitus, cardiovascular disease, asthma).

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Adjusted estimates for the association between maternal chronic diseases and adverse pregnancy outcomes stratified by parity

| Outcome                              | Normotensive women | Pregnancies with CH | Pregnancies with CKD | Pregnancies with CH and CKD |
|--------------------------------------|--------------------|---------------------|----------------------|-----------------------------|
|                                      | Cases, n (%) OR (95% CI) | Cases, n (%) OR (95% CI) | Cases, n (%) OR (95% CI) | Cases, n (%) OR (95% CI) |
| Preeclampsiaa                        |                    |                     |                      |                             |
| Primigravida                         | 53,339 (4.1)       | Reference           | 939 (17)             | 563 (5.7)                   | 1.37 (1.25–1.49) | 81 (16) | 2.66 (2.02–3.51) |
| Multigravida                         | 22,592 (1.6)       | Reference           | 999 (13)             | 416 (3.3)                   | 2.09 (1.88–2.32) | 94 (17) | 7.22 (5.55–9.40) |
| In-labor cesarean deliveryb          |                    |                     |                      |                             |
| Primigravida                         | 115,306 (11)       | Reference           | 948 (25)             | 1,134 (16)                  | 1.30 (1.21–1.38) | 95 (28) | 1.52 (1.13–2.05) |
| Multigravida                         | 60,775 (5)         | Reference           | 758 (13)             | 785 (8)                     | 1.41 (1.31–1.53) | 84 (21) | 2.39 (1.78–3.20) |
| Prelabor cesarean deliveryb          |                    |                     |                      |                             |
| Primigravida                         | 53,507 (5.6)       | Reference           | 505 (15)             | 703 (11)                    | 1.76 (1.62–1.90) | 93 (28) | 3.18 (2.34–4.34) |
| Multigravida                         | 95,692 (7.6)       | Reference           | 1,054 (17)           | 1,275 (12)                  | 1.52 (1.42–1.62) | 120 (26) | 2.33 (1.80–3.02) |
| Spontaneous preterm birth (<37 wk of gestation)b |                    |                     |                      |                             |
| Primigravida                         | 38,241 (3)         | Reference           | 183 (3.8)            | 373 (4)                     | 1.19 (1.07–1.32) | 23 (6) | 1.21 (0.77–1.90) |
| Multigravida                         | 29,551 (2.1)       | Reference           | 186 (2.6)            | 376 (3.1)                   | 1.30 (1.17–1.45) | 17 (3.9) | 1.17 (0.69–1.97) |
| Medically indicated preterm birth (<37 wk of gestation)b |                    |                     |                      |                             |
| Primigravida                         | 42,644 (3.4)       | Reference           | 649 (12)             | 553 (5.9)                   | 1.84 (1.68–2.01) | 137 (28) | 8.64 (6.91–10.8) |
| Multigravida                         | 30,291 (2.1)       | Reference           | 713 (9)              | 593 (4.9)                   | 2.28 (2.08–2.49) | 132 (24) | 9.30 (7.37–11.7) |
| Stillbirthb                          |                    |                     |                      |                             |
| Primigravida                         | 4685 (0.36)        | Reference           | 39 (0.72)            | 43 (0.44)                   | 1.12 (0.83–1.52) | 2 (0.39) | —                 |
| Multigravida                         | 4450 (0.31)        | Reference           | 59 (0.75)            | 51 (0.40)                   | 1.20 (0.90–1.59) | 5 (0.88) | 1.73 (0.73–4.13) |
| Small for gestational ageb           |                    |                     |                      |                             |
| Primigravida                         | 46,439 (3.6)       | Reference           | 552 (10)             | 448 (4.6)                   | 1.23 (1.12–1.36) | 69 (14) | 4.26 (3.28–5.54) |
| Multigravida                         | 23,763 (1.6)       | Reference           | 495 (6.3)            | 307 (2.4)                   | 1.37 (1.22–1.54) | 42 (7.4) | 4.99 (3.55–7.01) |

Total number of primiparous women=1,321,972; multiparous women=1,466,518.
BMI: body mass index; CH: chronic hypertension; CI: confidence interval; CKD: chronic kidney disease; OR: odds ratio.

* Adjusted for maternal age, educational level, smoking, BMI, country of origin, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), birth year, and child’s sex; ** Adjusted for maternal age, educational level, smoking, BMI, country of origin, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), and birth year.

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## SUPPLEMENTAL TABLE 4

Adjusted estimates for the association between maternal chronic diseases and adverse pregnancy outcomes stratified by maternal age

| Outcome | Normotensive women Cases, n (%) OR (95% CI) | Pregnancies with CH Cases, n (%) OR (95% CI) | Pregnancies with CKD Cases, n (%) OR (95% CI) | Pregnancies with CH and CKD Cases, n (%) OR (95% CI) |
|---------|---------------------------------------------|----------------------------------------------|-----------------------------------------------|--------------------------------------------------|
| Preeclampsia<sup>a</sup> |
| <35 y  | 64,375 (2.7) Reference 1293 (14) 4.78 (4.48–5.12) 779 (4.2) 1.58 (1.46–1.70) 111 (14) 3.59 (2.78–4.63) |
| ≥35 y  | 11,556 (2.9) Reference 645 (16) 4.48 (4.07–4.93) 200 (5.2) 1.79 (1.54–2.08) 64 (21) 6.17 (4.49–8.48) |
| In-labor cesarean delivery<sup>b</sup> |
| <35 y  | 140,217 (7.3) Reference 1003 (15) 4.48 (4.07–4.93) 1,484 (10) 1.37 (1.29–1.45) 110 (21) 1.77 (1.36–2.31) |
| ≥35 y  | 35,864 (12) Reference 703 (24) 1.81 (1.64–1.99) 435 (16) 1.33 (1.19–1.49) 69 (35) 2.28 (1.60–3.25) |
| Spontaneous preterm birth (<37 wk of gestation)<sup>b</sup> |
| <35 y  | 107,815 (5.7) Reference 828 (13) 1.91 (1.76–2.06) 1,410 (10) 1.63 (1.54–1.74) 136 (24) 2.94 (2.30–3.75) |
| ≥35 y  | 41,384 (13) Reference 731 (25) 1.78 (1.63–1.95) 568 (20) 1.51 (1.37–1.66) 77 (38) 2.47 (1.78–3.41) |
| Medically indicated preterm birth (<37 wk of gestation)<sup>b</sup> |
| <35 y  | 57,372 (2.5) Reference 246 (3.0) 1.08 (0.95–1.24) 618 (3.5) 1.25 (1.15–1.36) 31 (5.3) 1.31 (0.87–1.96) |
| ≥35 y  | 10,420 (2.7) Reference 123 (3.3) 1.06 (0.88–1.27) 131 (3.6) 1.22 (1.02–1.48) 9 (4.1) 0.88 (0.39–1.94) |
| Stillbirth<sup>b</sup> |
| <35 y  | 61,446 (2.7) Reference 833 (9.5) 3.79 (3.51–4.11) 916 (5.1) 2.04 (1.90–2.20) 179 (24) 8.93 (7.30–10.9) |
| ≥35 y  | 11,489 (3.0) Reference 529 (13) 4.27 (3.86–4.73) 230 (6.1) 2.08 (1.81–2.40) 90 (30) 9.76 (7.38–12.9) |
| Small for gestational age<sup>b</sup> |
| <35 y  | 7388 (0.31) Reference 60 (0.66) 1.75 (1.35–2.27) 69 (0.37) 1.10 (0.86–1.39) 4 (0.52) — |
| ≥35 y  | 1747 (0.44) Reference 38 (0.89) 1.67 (1.20–2.32) 25 (0.64) 1.39 (0.92–2.10) 3 (0.96) — |

Total number of pregnancies of mothers at the age of <35 years—2,384,532; pregnancies to mothers who were 35 years or older—403,958.

BMI, body mass index; CH, chronic hypertension; CKD, chronic kidney disease; CI, confidence interval; OR, odds ratio.

<sup>a</sup> Adjusted for educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), birth year, and child’s sex; <sup>b</sup> Adjusted for educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), and birth year.

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| Outcome                          | Normotensive women Cases, n (%) OR (95% CI) | Pregnancy with CH Cases, n (%) OR (95% CI) | Pregnancy with CKD Cases, n (%) OR (95% CI) | Pregnancy with CH and CKD Cases, n (%) OR (95% CI) |
|---------------------------------|--------------------------------------------|--------------------------------------------|---------------------------------------------|--------------------------------------------------|
| **Pre-eclampsia**               |                                            |                                            |                                             |                                                  |
| Underweight                     | 1387 (1.8) Reference                      | 16 (12) 7.46 (4.36–12.8)                  | 19 (2.7) 1.68 (1.06–2.67)                   | 1 (3.9) —                                       |
| Normal                          | 31,584 (2.3) Reference                    | 553 (13) 5.94 (5.39–6.55)                 | 400 (3.5) 1.66 (149–1.84)                   | 68 (15) 4.48 (3.21–6.25)                        |
| Overweight                      | 16,139 (3.5) Reference                    | 450 (14) 4.16 (3.73–4.65)                 | 228 (5.4) 1.65 (1.43–1.90)                   | 35 (16) 3.36 (2.14–5.26)                        |
| Obese                           | 10,522 (5.8) Reference                    | 515 (18) 3.14 (2.82–3.49)                 | 141 (7.4) 1.38 (1.15–1.65)                   | 43 (26) 4.26 (2.85–6.37)                        |
| **In-labor cesarean delivery**  |                                            |                                            |                                             |                                                  |
| Underweight                     | 3579 (5.5) Reference                      | 15 (14) 2.43 (1.37–4.30)                  | 42 (7.8) 1.20 (0.86–1.66)                   | 3 (14) —                                       |
| Normal                          | 81,779 (7.2) Reference                    | 458 (14) 1.77 (1.59–1.97)                 | 855 (10) 1.34 (1.24–1.45)                   | 65 (20) 1.44 (0.98–2.13)                        |
| Overweight                      | 37,898 (10) Reference                     | 453 (20) 1.69 (1.50–1.90)                 | 454 (14) 1.42 (1.28–1.58)                   | 47 (33) 2.52 (1.61–3.93)                        |
| Obese                           | 20,492 (14) Reference                     | 513 (25) 1.49 (1.33–1.66)                 | 271 (19) 1.38 (1.20–1.60)                   | 42 (38) 2.05 (1.29–3.25)                        |
| **Prelabor cesarean delivery**  |                                            |                                            |                                             |                                                  |
| Underweight                     | 3491 (5.3) Reference                      | 8 (8.0) 1.04 (0.50–2.18)                  | 49 (8.9) 1.50 (1.10–2.05)                   | 4 (17) —                                       |
| Normal                          | 69,816 (6.2) Reference                    | 428 (14) 1.75 (1.57–1.96)                 | 932 (11) 1.66 (1.54–1.79)                   | 87 (25) 2.57 (1.87–3.52)                        |
| Overweight                      | 29,760 (8.3) Reference                    | 390 (17) 1.68 (1.45–1.89)                 | 383 (12) 1.44 (1.28–1.62)                   | 48 (34) 2.57 (1.67–3.96)                        |
| Obese                           | 15,543 (11) Reference                     | 378 (19) 1.38 (1.21–1.56)                 | 232 (17) 1.43 (1.22–1.67)                   | 31 (31) 2.21 (1.38–3.53)                        |
| **Spontaneous preterm birth (<37 wk of gestation)** | |  | | |
| Underweight                     | 2100 (2.8) Reference                      | 3 (2.5) —                                  | 36 (5.4) 1.49 (1.07–2.09)                   | 1 (4.4) —                                       |
| Normal                          | 33,143 (2.4) Reference                    | 133 (3.3) 1.28 (1.07–1.53)                 | 349 (3.2) 1.18 (1.06–1.32)                   | 18 (5.0) 1.12 (0.66–1.90)                       |
| Overweight                      | 12,195 (2.7) Reference                    | 92 (3.2) 1.06 (0.85–1.31)                 | 130 (3.3) 1.13 (0.93–1.36)                   | 6 (3.8) 0.74 (0.32–1.75)                        |
| Obese                           | 5481 (3.1) Reference                      | 86 (3.4) 0.99 (0.79–1.24)                 | 80 (3.4) 1.40 (1.11–1.76)                   | 2 (1.6) —                                       |
| **Medically indicated preterm birth (<37 wk of gestation)** |  |  |  | |
| Underweight                     | 796 (3.7) Reference                      | 17 (13) 5.17 (3.05–8.76)                  | 35 (5.3) 1.70 (1.19–2.44)                   | 3 (12) —                                       |
| Normal                          | 30,288 (2.2) Reference                    | 370 (8.7) 4.10 (3.65–4.61)                 | 483 (4.4) 2.12 (1.92–2.32)                   | 103 (23) 8.93 (0.77–1.18)                       |
| Overweight                      | 9588 (2.1) Reference                      | 298 (10) 4.08 (3.58–4.66)                 | 201 (4.9) 2.27 (1.95–2.64)                   | 56 (27) 8.84 (5.93–13.2)                        |
| Obese                           | 4997 (2.8) Reference                      | 322 (11) 3.54 (3.10–4.04)                 | 103 (5.6) 1.86 (1.52–2.28)                   | 43 (26) 7.24 (4.91–10.7)                        |
| **Stillbirth**                  |                                            |                                            |                                             |                                                  |
| Underweight                     | 165 (0.21) Reference                      | 1 (0.73) —                                  | 3 (0.43) —                                   | 0 (0.0) —                                       |
| Normal                          | 3514 (0.25) Reference                     | 25 (0.57) 2.05 (1.38–3.05)                 | 29 (0.26) 0.96 (0.67–1.39)                   | 2 (0.4) —                                       |

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### SUPPLEMENTAL TABLE 5

Adjusted estimates for the association between maternal chronic diseases and adverse pregnancy outcomes stratified by maternal body mass index (continued)

| Outcome                      | Normotensive women | Pregnancy with CH | Pregnancy with CKD | Pregnancy with CH and CKD |
|------------------------------|--------------------|-------------------|-------------------|--------------------------|
|                              | Cases, n (%) OR (95% CI) | Cases, n (%) OR (95% CI) | Cases, n (%) OR (95% CI) | Cases, n (%) OR (95% CI) |
| Overweight                   | 1699 (0.37) Reference | 18 (0.56) 1.33 (0.84—2.12) | 25 (0.60) 1.51 (1.00—2.28) | 0 — |
| Obese                        | 1002 (0.55) Reference | 33 (1.1) 1.78 (1.23—2.54) | 11 (0.57) 0.95 (0.52—1.72) | 2 (1.2) — |
| Small for gestational aged   |                    |                   |                   |                          |
| Underweight                  | 3719 (4.7) Reference | 18 (13) 3.44 (2.05—5.79) | 40 (5.7) 1.11 (0.80—1.53) | 3 (12) — |
| Normal                       | 34,134 (2.4) Reference | 375 (8.6) 3.91 (3.50—4.37) | 364 (3.2) 1.27 (1.13—1.41) | 49 (11) 4.53 (3.29—6.24) |
| Overweight                   | 9451 (2.1) Reference | 212 (6.6) 3.52 (3.04—4.07) | 110 (2.6) 1.22 (1.00—1.49) | 18 (8.3) 5.19 (3.09—8.70) |
| Obese                        | 4082 (2.2) Reference | 176 (6.1) 2.80 (2.37—3.30) | 67 (3.5) 1.55 (1.21—1.99) | 9 (5.4) 2.70 (1.37—5.32) |

*BM*II body mass index; *CH*, chronic hypertension; *CI*, confidence interval; *CKD*, chronic kidney disease; *OR*, odds ratio.

a Adjusted for maternal age, educational level, smoking, country of origin, parity, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), birth year, and child’s sex; b Underweight (BMI, <18.5 kg/m²); c Normal (BMI, ≥18.5 to <25 kg/m²); d Overweight (BMI ≥25 to <30 kg/m²); e Obese (BMI, ≥30 kg/m²); f Adjusted for maternal age, educational level, smoking, country of origin, parity, other comorbidities (diabetes mellitus, cardiovascular disease, asthma), and birth year.

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### SUPPLEMENTAL TABLE 6
The association between maternal chronic diseases and perinatal outcomes after excluding women with comorbidities (singleton pregnancies in 1982–2012)

| Outcome                                           | Pregnancies of normotensive women (n=2,608,565) | Chronic hypertension (CH) (n=11,550) | Chronic kidney disease (CKD) (n=20,012) | CH and CKD (n=716) |
|---------------------------------------------------|-------------------------------------------------|-------------------------------------|----------------------------------------|--------------------|
| Preeclampsia                                      | Reference                                       | Adjusted OR (95% CI)<sup>a</sup> | 4.97 (4.69–5.27)                       | 1.61 (1.49–1.74)   | 7.37 (5.93–9.14) |
| In-labor cesarean delivery                        | Reference                                       | Adjusted OR (95% CI)<sup>a</sup> | 1.74 (1.63–1.86)                       | 1.35 (1.27–1.42)   | 2.79 (2.20–3.54) |
| Prelabor cesarean delivery                        | Reference                                       | Adjusted OR (95% CI)<sup>a</sup> | 1.76 (1.65–1.88)                       | 1.57 (1.48–1.66)   | 3.76 (3.01–4.70) |
| Spontaneous preterm birth (<37 wk)                | Adjusted OR (95% CI)<sup>b</sup>               | 1.10 (0.97–1.23)                    | 1.24 (1.14–1.35)                       | 1.70 (1.09–2.67)   |
| Medically indicated preterm birth (<37 wk)        | Adjusted OR (95% CI)<sup>b</sup>               | 4.11 (3.85–4.41)                    | 1.094 (1.81–2.09)                      | 12.5 (10.22–15.3)  |
| Stillbirth                                         | Adjusted OR (95% CI)<sup>b</sup>               | 1.66 (1.35–2.09)                    | 1.19 (0.95–1.49)                       | 1.52 (0.56–4.07)   |
| Small for gestational age                          | Adjusted OR (95% CI)<sup>b</sup>               | 3.62 (3.37–3.89)                    | 1.25 (1.15–1.36)                       | 5.38 (4.27–6.80)   |

A total of 147,647 records with comorbidities (DM, CVD, or asthma) were deleted from these analyses. All adjusted estimates cluster on mothers’ ID.

CH, chronic hypertension; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; ID, identity document; OR, odds ratio.

<sup>a</sup> Adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, birth year, and child’s sex; <sup>b</sup> Adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, and birth year.

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