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# Kidney function and future risk for adverse pregnancy outcomes: a population-based study from HUNT II, Norway

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## Abstract

**Background.** Current knowledge on prepregnancy reduced kidney function and the risk of adverse pregnancy outcomes mainly relies on small studies in selected populations. We aim to investigate whether reduced kidney function is associated with the risk of adverse pregnancy-related outcomes in the general population.

**Methods.** A population-based study linking all women attending the Second Health Study in Nord-Trøndelag, Norway (1995–97) and subsequent pregnancies registered in the Medical Birth Registry. Multivariable random-effect logistic regression analysis was used to explore the association between renal function and study outcome.

**Results.** The mean eGFR among 3405 women was 107.6 ± 19.4 ml/min/1.73 $m^2$ at baseline; 18.8% and 0.1% had eGFR of 60–89 and <60, respectively. Over the next 11 years, they gave birth to 5655 singletons of whom 885 (17.7%) were complicated with preeclampsia, small for gestational age (SGA) or preterm birth. Women with eGFR 60–89 were not at increased risk for this combined outcome compared to women with eGFR ≥90, although women with eGFR 60–74 tended to have an increased risk. Neither was reduced kidney function a risk factor among women with microalbuminuria, but those with an eGFR of 60–89 plus hypertension had a significantly increased risk: odds ratios for preeclampsia, SGA or preterm birth were 2.58 (95% CI 1.40–4.75, $P < 0.001$) and 10.09 (95% CI 2.38–42.87, $P < 0.001$) in hypertensive women with eGFR 75–89 and 60–74, respectively. Relative excess risk due to interaction between reduced kidney function and hypertension was 2.23 (95% CI 1.35–3.10, $P < 0.001$). Women with a reduced kidney function were not at increased risk for other pregnancy complications like caesarean section, maternal bleeding, dystocia, pre-labour rupture of membranes, Apgar score ≤7, stillbirth or congenital malformations.

**Conclusions.** Women with eGFR 60–89 ml/min/1.73 $m^2$ were not at increased risk for preeclampsia, SGA or preterm birth unless they were also hypertensive.

**Keywords:** glomerular filtration rate; mild reduced kidney function; population-based cohort study; pregnancy outcome

## Introduction

Pregnancy imposes significant stress on the kidneys, resulting in an increased risk for maternal as well as fetal complications in subjects with established moderate-to-serious

chronic kidney disease (CKD) [1–3]. The prevalence of mild reduced kidney function [i.e. estimated glomerular filtration rate (eGFR) 60–89 ml/min per 1.73 $m^2$] in a general population of pre-pregnant women could potentially be high, and it is unknown whether these women are at increased risk for adverse pregnancy outcomes [4,5].

Small studies on pregnancies in women with moderate to severe reduced kidney function (eGFR <60 ml/min per 1.73 $m^2$) have demonstrated a substantially increased risk for adverse pregnancy outcomes [6–10]. Preeclampsia, hypertension (HT), caesarean delivery and further deterioration of the kidney function are common maternal complications. The offsprings were frequently born preterm or small for gestational age (SGA) [6]. Overall fetal loss rates were also increased compared to the general population, and stillbirths occurred in 4–8% [8,11].

GFR is widely accepted as the best overall measure of kidney function. However, in the early stages of CKD, other signs of kidney damage like proteinuria, haematuria, radiological or histological signs should also be present. However, in the K/DOQI guidelines, it was also discussed if high blood pressure (BP) should be included in the definition of CKD [12]. A complex and close interaction between glomerular filtration, HT and microalbuminuria in young adults is reported [13].

To our knowledge, no population studies have prospectively evaluated the influence of varying degrees of prepregnancy reduced kidney function on the risk of adverse pregnancy outcomes. The present study used data from 3405 women who attended the second Nord-Trøndelag Health Study (HUNT 2) and who later became pregnant. The aims were to (1) estimate the prevalence of reduced kidney function in a general population of pre-pregnant women, and (2) investigate whether reduced prepregnancy eGFR alone or in combination with microalbuminuria or HT, respectively, is associated with subsequent adverse pregnancy-related outcomes.

## Subjects and methods

### *Study population*

The HUNT 2 Study was conducted from 1995 to 1997 in the county of Nord-Trøndelag, Norway. All inhabitants aged 20 years and older were invited to participate, and 66 149 (71.2%) accepted the invitation. The population was ethnically homogeneous (>97% whites). The objectives, methods and participation in the HUNT 2 Study are described in detail elsewhere [14]. The unique 11-digit national personal number was used to link women attending the HUNT 2 Study to information in the Medical Birth Registry of Norway on all pregnancies from 1 August 1995 to 31 December 2005 [15]. All participants gave an informed consent before the examination, and the study was approved by the Regional Committee of Ethics in Medical Research and the Norwegian Data Inspectorate.

### *Clinical and laboratory measurements*

BP was measured three times with an oscillometric device (Dinamap 845XT; Criticon, Tampa, FL, USA) by trained nurses or technicians with cuff size adjusted for the arm circumference. The average of the last two measurements was used in the present study. Standardized measurements of height and weight were performed and used for calculation of the body mass index (BMI). From the questionnaire, we obtained information on diabetes, smoking status, education, history of cardiovascular diseases (CVD) and family history of CVD. Fresh serum and urine samples were analysed within 2 days on a Hitachi 911 autoanalyser (Hitachi, Mito, Japan) applying reagents from Roche (Roche Diagnostics, Mannheim, Germany). Serum creatinine was measured using a blank-rate Jaffé method and later recalibrated for use with the isotope dilution mass spectrometry (IDMS)-traceable four-variable Modification of Diet in Renal Disease (MDRD) Study equation [16,17]: GFR (ml/min/1.73 $m^2$) = 175 × serum creatinine $(mg/dl)^{-1.154}$ × $age^{-0.203}$ × 0.742 (in women). Urinary samples were measured in a subpopulation with diabetes and treated HT, plus a 5% random sample. These were collected through three consecutive mornings, and those with ongoing menstruation or urinary tract infection the last week before collection were excluded. Urine albumin was measured by an immunoturbidimetric method (Dako A/S, Glostrup, Denmark), and urine albumin–creatinine ratio (ACR) was used as an expression for albumin excretion. For women, micro- and macroalbuminuria were defined as ACR ≥3.5 mg/mmol and ≥35 mg/mmol, respectively [18].

Kidney function was graded as eGFR (ml/min per 1.73 $m^2$) ≥90, 75–89, 60–74 and <60 [19,20]. We also graded kidney function according to the K/DOQI guidelines as stage 1 (eGFR ≥90 plus persistent microalbuminuria), stage 2 (eGFR 60–89 plus persistent microalbuminuria) or stages 3–5 (eGFR <60). In the K/DOQI report, it was also discussed if the kidney function should be graded according to eGFR and the presence or absence of HT; hence we computed eGFR ≥90 plus HT, 75–89 plus HT and 60–74 plus HT [12]. Due to an annual decline in the kidney function, the prevalence estimates of CKD are only based on women giving birth in the period 1995–97.

In the Medical Birth Registry of Norway, preeclampsia and gestational HT are considered as two separate diagnoses. We only included women with preeclampsia, which is defined according to international classifications as a sustained increase in BP to at least 140/90 mmHg after 20 weeks of gestation together with proteinuria of at least +1 or more on a semi-quantitative dipstick. Birth weight was expressed as a standard deviation score (BW-SDS) to correct for gestational age and sex using standards estimated from the Medical Birth Registry for the period 1988–98 [21]. SGA was defined as a birth weight less than the 10th percentile for gestational age (< −1.3 SD). Preterm birth was defined as delivery before the 37th gestational week. Our main adverse outcome was defined as preeclampsia, preterm birth or SGA.

### *Statistical analysis*

Data were analysed in a cohort design with reduced kidney function as the main exposure and pregnancy-related complications as outcome variables using Stata software, version 10.1 (StataCorp, College Station, TX, USA). In all, we identified 6460 births with gestational age >22 weeks or birth weight above 500 g during the follow-up period. We excluded 11 women without clinical data, 264 twin pregnancies and 530 women who delivered within 9 months after attending HUNT 2 as the latter could have biased eGFR, BMI, etc. at the examination. All together, we included 3405 women with 5655 singleton births in the final analysis. Binary logistic regression analysis was used to calculate crude and multi-adjusted odds ratio (OR) for study outcomes. In the multi-adjusted analysis, we controlled for time interval from baseline measurements to the index birth, parity (0, 1, ≥2), previous preeclampsia, preterm birth or SGA, and other maternal risk factors as age, BP, BMI, diabetes, smoking, educational level, history of CVD and family history of CVD. We used a random-effect regression model to account for multiple deliveries from the same mother (correlated outcome).

A potential interaction between eGFR and microalbuminuria or HT, respectively, was explored as departure from additivity of effects [22]. The relative excess risk for adverse outcomes due to interaction (RERI) was calculated: $RERI = OR\ (ab) - OR\ (\bar{a}b) - OR\ (a\bar{b}) + 1$, where $OR\ (ab)$ denotes the OR among those exposed to both factors, and $OR\ (\bar{a}\bar{b})$ is used as a reference category ($OR = 1.0$). Ninety-five percent confidence intervals (CIs) for interactions were calculated as proposed by Hosmer and Lemeshow [23].

Fractional polynomials were used to predict adjusted risk (probabilities) for adverse outcomes as a continuous function of eGFR. The analyses were repeated for those with HT and those with microalbuminuria. We adjusted for maternal age and parity that are the two most important covariates.

In general, there were few missing data (<2% for most variables). However, ACR was by design only measured in 15% of the women attending HUNT 2, and was therefore mainly 'missing at random' [24]. The missing values were handled using multiple imputation, now conceded a standard method for handling missing data [25,26]. Multiple imputation estimates the mean and uncertainty of the missing data from the observed

**Table 1.** Baseline characteristics of the women at HUNT 2 (1995–1997)

| | All women ($n = 3405$) |
|---|---|
| Mean age ± SD in HUNT 2 (years) | 26.1 ± 4.4 |
| Mean maternal age ± SD at delivery (years) | 30.8 ± 4.3 |
| Parity when attending HUNT 2, *n* (%) | |
| 0 | 1085 (31.9) |
| 1 | 1180 (34.6) |
| ≥2 | 1140 (33.5) |
| University or college degree, *n* (%) | 1238 (36.3) |
| Smoking history, *n* (%) | |
| Current | 927 (27.2) |
| Former | 428 (12.6) |
| Never | 2050 (60.2) |
| Family history of cardiovascular disease, *n* (%) | 1341 (39.4) |
| Diabetes mellitus, *n* (%) | 10 (0.3) |
| History of cardiovascular disease, *n* (%) | 5 (0.1) |
| Mean body weight ± SD (kg) | 67.7 ± 11.6 |
| Mean body mass index ± SD (kg/m$^2$) | 24.3 ± 3.9 |
| Mean systolic blood pressure ± SD (mmHg) | 120.6 ± 11.2 |
| Mean diastolic blood pressure ± SD, mmHg | 70.9 ± 8.3 |
| Albuminuria | |
| Mean albumin creatinine ratio ± SD (mg/mmol) | 0.86 ± 1.27 |
| Microalbuminuria, *n* (%) | 110 (3.2) |
| Macroalbuminuria, *n* (%) | 0 (0.0) |
| Kidney function | |
| Mean serum creatinine ± SD (μmol/l) | 60.5 ± 9.4 |
| Mean eGFR ± SD (ml/min/1.73 m$^2$) | 107.6 ± 19.4 |

values by using a simulation-based approach. We used information from all measured ACR values in the imputation model ($n = 9738$). Each missing value is replaced by $m > 1$ simulated values. The resulting $m$ complete data sets can then be analysed by a standard complete data method, and the results are combined to produce inferential statements (e.g. interval estimates or *P*-values) that incorporate missing data uncertainty. We used $m = 20$ imputations to achieve maximum accuracy [25].

## Results

Over an 11-year period, 3405 women gave birth to 5655 singletons (mean time 4.7 ± 2.5 years after the HUNT 2 Study). In all, we identified 885 (17.7%) cases with our main study outcomes (preeclampsia, $n = 204$; small for gestational age, $n = 537$; preterm birth, $n = 285$). The characteristics of the women who attended the HUNT 2 Study and subsequently became pregnant are presented in Table 1. The mean eGFR was 107.6 ± 19.4 ml/min/1.73 m$^2$ and microalbuminuria calculated by multiple imputation was present in 3.2% of the women. The overall prevalence of CKD was 3.3%, and CKD stages 1, 2 and 3 occurred in 2.4%, 0.8% and 0.1%, respectively. No women with CKD 4 or 5 gave birth during the follow-up period.

Table 2 shows maternal and fetal complications by categories of eGFR. Pregnancy duration was significantly lower in the eGFR category 60–74 compared to eGFR ≥90 ($P = 0.05$). The corresponding difference was not significant for the eGFR category 75–89. Women with eGFR 60–89 were not at increased risk for low birth weight, preeclampsia, caesarean delivery, maternal bleeding, dystocia, pre-labour rupture of membranes, Apgar score ≤7, stillbirth or congenital malformations compared to those with eGFR ≥90.

Table 3 presents multi-adjusted OR for our main study outcomes (preeclampsia, SGA and preterm birth) alone or combined by categories of eGFR. Women with eGFR 60–89 showed no increased risk for preeclampsia or SGA compared to eGFR ≥90. In women with eGFR <60, the OR for preeclampsia was almost 11, but the estimate was not robust as only one woman had preeclampsia. Preterm birth risk in women with an eGFR of 60–74 was significantly increased (OR 2.69, 95% CI 1.38–5.24, $P = 0.004$). The OR for the combined adverse pregnancy outcome increased with decreasing eGFR and the estimate tended towards significance in the eGFR category 60–74 ($P = 0.066$).

Table 4 presents the risk for preeclampsia, SGA or preterm birth by kidney function and blood pressure. The reference category was eGFR ≥90 and BP <140/90 mmHg. The OR increased from 1.82 (95% CI 1.12–2.97, $P = 0.015$) in women with HT and eGFR ≥90 to 4.24 (95% CI 1.89–9.50, $P < 0.001$) in women with HT and eGFR <90. The additive interaction between eGFR and HT defined as relative excess risk due to interaction (RERI) was explored. Women with eGFR <90 and HT had a multi-adjusted RERI of 2.23 (95% CI 1.35–3.10, $P < 0.001$). As a RERI of 0 means no interaction, a RERI of 2.23 indicates that the OR for an adverse pregnancy outcome is 2.23 higher than expected based on the addition of the two risk factors.

OR for preeclampsia, SGA or preterm birth was 2.58 (95% CI 1.40–4.75, $P < 0.001$) in hypertensive women with eGFR 75–89, and 10.09 (95% CI 2.38–42.87, $P < 0.001$) in women with eGFR 60–74 compared to women with eGFR ≥90 and no HT. There was no significant interaction between eGFR and microalbuminuria (RERI 1.70, 95% CI −1.95–5.34, $P = 0.36$), and these women were not at increased risk for preeclampsia, SGA or preterm birth.

Figure 1 illustrates the risk of preeclampsia, SGA or preterm birth as a continuous function of eGFR (1A), eGFR plus microalbuminuria (1B) and eGFR plus HT (1C). Figure 1A and C display a U-shaped configuration implying increased risk for adverse outcomes associated with both decreased and increased glomerular filtration. The probability increased significantly from 0.20 to 0.27 as eGFR decreased from 105 to 65 ml/min/1.73 m$^2$ (Figure 1A). The corresponding risk was not increased in women with microalbuminuria (Figure 1B). The risk increased steeply from 0.25 to 0.48 for hypertensive women when eGFR decreased from 105 to 70 ml/min/1.73 m$^2$ (Figure 1C).

## Discussion

In this large population-based study, we investigated whether reduced kidney function was associated with subsequent adverse pregnancy-related outcomes. The principal findings were that the risk for preeclampsia or SGA offspring was not increased in women with a reduced kidney function graded as eGFR 60–89 ml/min/1.73 m$^2$ or eGFR 60–89 ml/min/1.73 m$^2$ plus microalbuminuria. The risk of preterm birth was, however, increased two to three times. There was a strong and graded risk increase for preeclampsia, SGA or preterm birth when women with eGFR 60–89 ml/min/1.73 m$^2$ were also hypertensive. Furthermore, an important synergistic effect of reduced eGFR and HT was observed, implying an increased risk for these pregnancy outcomes in women with both reduced eGFR and HT.

**Table 2.** Pregnancy and fetal outcomes by baseline eGFR

| | eGFR (ml/min/1.73 $m^2$) | | | |
|---|---|---|---|---|
| | ≥90 | 75–89 | 60–74 | <60 |
| *N* (% of all pregnancies) | 4656 (82.3) | 867 (15.3) | 126 (2.2) | 6 (0.1) |
| Mean eGFR ± SD (ml/min/1.73 $m^2$) | 113.0 (16.8) | 84.2 (4.0) | 71.1 (3.3) | 56.8 (3.6) |
| Mean maternal age ± SD at delivery (years) | 30.9 ± 4.3 | 32.0 ± 4.5[a] | 33.0 ± 4.1[a] | 34.1 ± 4.5 |
| Mean birth weight ± SD (g) | 3611.1 ± 605.7 | 3602.8 ± 587.9 | 3505.1 ± 669.3 | 4054.7 ± 338.3 |
| Mean pregnancy duration ± SD (days) | 279.0 ± 14.9 | 278.9 ± 14.0 | 274.5 ± 18.8[b] | 284.4 ± 5.2 |
| Preterm delivery week 34–37, *n* (%) | 144 (3.1) | 34 (3.9) | 10 (7.9) | 0 (0) |
| Preterm delivery <34 weeks, *n* (%) | 80 (1.7) | 14 (1.6) | 3 (2.4) | 0 (0) |
| SGA (*z*-score, 3rd–10th percentile), *n* (%) | 369 (7.9) | 85 (9.8) | 12 (9.5) | 0 (0) |
| VSGA (*z*-score, <3rd percentile), *n* (%) | 61 (1.3) | 9 (1.0) | 1 (0.8) | 0 (0) |
| Preeclampsia ≥ week 34, *n* (%) | 152 (3.3) | 31 (3.6) | 3 (2.4) | 1 (16.7) |
| Preeclampsia < week 34, *n* (%) | 14 (0.3) | 3 (2.4) | 0 (0) | 0 (0) |
| Congenital malformation, *n* (%) | 96 (2.1) | 17 (2.0) | 5 (4.0) | 0 (0) |
| Cesarean section, *n* (%) | 166 (3.6) | 34 (3.9) | 3 (2.4) | 1 (16.7) |
| Elective | 218 (4.7) | 42 (4.8) | 3 (2.4) | 0 (0) |
| Acute | 252 (5.4) | 53 (6.1) | 10 (7.9) | 1 (16.7) |
| Dystoci, *n* (%) | 652 (14.0) | 112 (12.9) | 16 (12.7) | 0 (0) |
| Premature rupture of membrane, *n* (%) | 189 (4.1) | 36 (4.2) | 5 (4.0) | 0 (0) |
| Bleeding >500 ml, *n* (%) | 350 (7.5) | 65 (7.5) | 14 (11.1) | 0 (0) |
| Apgar score <7 after 5 min, *n* (%) | 43 (0.9) | 5 (0.6) | 3 (2.4) | 0 (0) |

SGA, small for gestational age; VSGA, very small for gestational age.
Pregnancy and fetal outcomes rely on all ($n = 5655$) pregnancies after HUNT 2. Except in the first line, percentages are within the eGFR group (column). Significantly different.
[a]$P < 0.001$ and [b]$P = 0.05$, respectively, compared to eGFR ≥ 90 ml/min/1.73 $m^2$.

**Table 3.** Odds ratio for main study outcomes by estimated GFR

| | Odds ratio (95% CI, *P*-value) | | |
|---|---|---|---|
| | Crude estimate | Multi-adjusted estimate[a] | *P* for trend |
| Preeclampsia ($n = 204$) | | | |
| eGFR | | | |
| ≥90 ($n = 166$) | 1.0 (ref.) | 1.0 (ref.) | 0.99 |
| 75–89 ($n = 34$) | 1.12 (0.75–1.66, $P = 0.58$) | 0.98 (0.63–1.51, $P = 0.92$) | |
| 60–74 ($n = 3$) | 0.66 (0.20–2.20, $P = 0.50$) | 0.69 (0.20–2.41, $P = 0.56$) | |
| <60 ($n = 1$) | 5.74 (0.48–68.10, $P = 0.17$) | 10.78 (0.83–140.75, $P = 0.070$) | |
| Preterm birth ($n = 285$) | | | |
| eGFR | | | |
| ≥90 ($n = 224$) | 1.0 (ref.) | 1.0 (ref.) | 0.08 |
| 75–89 ($n = 48$) | 1.16 (0.82–1.64, $P = 0.40$) | 1.03 (0.72–1.48, $P = 0.86$) | |
| 60–74 ($n = 13$) | 2.39 (1.24–4.62, $P = 0.009$) | 2.69 (1.38–5.24, $P < 0.004$) | |
| <60 ($n = 0$) | n.a. | n.a. | |
| SGA ($n = 565$) | | | |
| eGFR | | | |
| ≥90 ($n = 430$) | 1.0 (ref.) | 1.0 (ref.) | 0.29 |
| 75–89 ($n = 94$) | 1.21 (0.91–1.62, $P = 0.19$) | 1.14 (0.86–1.52, $P = 0.35$) | |
| 60–74 ($n = 13$) | 1.18 (0.58–2.40, $P = 0.65$) | 1.29(0.66–2.51, $P = 0.45$) | |
| <60 ($n = 0$) | n.a. | n.a. | |
| Preeclampsia or SGA or preterm birth ($n = 885$) | | | |
| eGFR | | | |
| ≥90 ($n = 706$) | 1.0 (ref.) | 1.0 (ref.) | 0.054 |
| 75–89 ($n = 153$) | 1.25 (0.96–1.62, $P = 0.091$) | 1.13 (0.90–1.45, $P = 0.35$) | |
| 60–74 ($n = 25$) | 1.54 (0.83–2.88, $P = 0.17$) | 1.65 (0.97–2.83, $P = 0.066$) | |
| <60 ($n = 1$) | 1.04 (0.06–19.02, $P = 0.98$) | 2.53 (0.25–25.35, $P = 0.43$) | |

SGA, small for gestational age; n.a., data not available.
[a]Adjusted for maternal age, parity, follow-up time, previous preeclampsia, preterm birth or SGA, systolic BP, BMI, diabetes, smoking, history of CVD, family history of CVD and education.
The estimates are based on all ($n = 5655$) pregnancies after HUNT 2. eGFR is expressed as ml/min/1.73 $m^2$.

**Table 4.** Odds ratio for preeclampsia, SGA or preterm birth by kidney function and blood pressure

| | Odds ratio (95% CI, *P*-value) | |
|---|---|---|
| | eGFR ≥90 | eGFR <90 |
| BP <140/90 mmHg | 1.0 (ref.) ($n = 4352$) | 1.18 (0.85–1.63, $P = 0.31$) ($n = 906$) |
| BP ≥140/90 mmHg or treated | 1.82 (1.12–2.97, $P = 0.015$) ($n = 304$) | 4.24 (1.89–9.50, $P < 0.001$) ($n = 93$) |
| RERI = 2.23 (1.35–3.10, $P < 0.001$) | | |

SGA, small for gestational age; BP, blood pressure; RERI, relative excess risk due to interaction.
The estimates were adjusted for maternal age, parity, follow-up time, previous preeclampsia, preterm birth or SGA, BMI, diabetes, smoking, history of CVD, family history of CVD, and education. The estimates are based on all ($n = 5655$) pregnancies after HUNT 2.

The prevalence of reduced kidney function among prepregnant women in the general population is unknown. Estimates for severe impaired kidney function range from 0.03% to 0.12% and are based on small, selected study populations [6,27,28]. The information was obtained from medical records and most women with mild CKD therefore remained undetected [29,30]. We found a prepregnancy prevalence of CKD of 3.3% in this population-based study, which is close to the age-adjusted prevalence of CKD in the general population [4,5]. We also confirmed prior assumptions that severe kidney disease is extremely rare in prepregnancy as none of almost 5700 pregnancies occurred in women with CKD 4 or 5. However, it is known that early pregnancy losses more frequently occur in the setting of kidney disease [31].

The risk of adverse pregnancy outcomes in CKD has been described in several small studies. Jones and Hayslett evaluated 82 pregnancies with CKD stages 3–5 and reported a prematurity rate of 59%, while 37% of the offspring were growth restricted. The infant mortality rate at delivery or within the first week was 7%. [8]. Cunningham *et al*. evaluated 37 pregnancies complicated by moderate and severe renal insufficiency and found that 58% and 64%, respectively, had preeclampsia [6]. In contrast, Bar *et al*. evaluated 46 pregnancies in women with primary renal disease where nearly 90% had serum creatinine <1.4 mg/dl. Preeclampsia and preterm delivery were reported in 22% and 23% of the pregnancies, respectively, while 13% were born growth restricted. They reported no stillbirths, and the overall pregnancy complication rate ranged from 4% to 22% [7]. In our population-based study that mainly included women with reduced kidney function measured at screening, the risk for adverse pregnancy outcomes was even lower. We found an overall prevalence of preeclampsia, SGA or preterm birth of 17.9% in women with eGFR <90 ml/min/1.73 $m^2$.

The risk for adverse pregnancy outcomes could depend on how reduced kidney function is defined. The level of GFR is widely accepted as the best overall measure of kidney function, but estimating kidney function is a rather difficult topic, especially in the near-normal range [17]. It is therefore recommended that other signs of kidney damage should be present for staging mild reduced kidney function [12]. Hence, we explored the association between eGFR alone and eGFR in combination with microalbuminuria or HT, respectively, and the pregnancy outcome risk. Firstly, when studying eGFR alone, the risk for preeclampsia, SGA or preterm birth increased by 50% as eGFR decreased from 105 to 60 ml/min/1.73 $m^2$ (Figure 1A), and the U-shaped configuration on the curve implies an increased risk for adverse outcomes in subjects with glomerular hyperfiltration as well. Glomerular hyperfiltration can be an early sign of kidney damage [13], but the accuracy of eGFR in the range ≥90 ml/min/1.73 $m^2$ is rather low, so the association should therefore be interpreted with caution [17]. Secondly, when mild reduced kidney function was graded in accordance with prevailing guidelines as eGFR plus microalbuminuria, we found no association with adverse outcomes (Figure 1B). However, there were few women with microalbuminuria, and the CIs are therefore wide. Microalbuminuria is an important predictor for future CVD [32,33], and risk factors for CVD have recently been found to be important for preeclampsia as well [34]. It is therefore no reason to conclude that microalbuminuria is not a risk factor for adverse pregnancy outcome. Thirdly, elevated BP is both a cause and a complication to kidney failure, and it has been discussed if HT should be included in the definition of mild reduced kidney function [12]. A recent review article concluded that adverse pregnancy outcome risk is strongly related to presence of HT in addition to the degree of renal insufficiency [35]. Our data support this conclusion as we found a strong and graded risk for preeclampsia, SGA and preterm birth in hypertensive women with reduced eGFR (Figure 1C). Furthermore, the important synergistic effect of reduced eGFR and HT imply an additional risk for these outcomes beyond the separate effects of reduced glomerular filtration and BP (Table 4). The close interaction between BP and glomerular filtration is mediated through a wide range of haemodynamic, metabolic and inflammatory mechanisms [36,37].

The clinical implications of this and related studies are several. Adverse outcomes due to impaired kidney function should be prevented through early identification and treatment. As more than 15% of the women in reproductive age have a mild reduced GFR, it is important to identify those with risk factors of clinical significance. We found that women with eGFR 60–89 ml/min/1.73 $m^2$ were not at increased risk for adverse pregnancy outcomes unless they were also hypertensive. These women, however, should be closely monitored during the pregnancy. Furthermore, they should also be evaluated for lifestyle intervention and/or pharmacological treatment after pregnancy to prevent a further decline in the kidney function as a recent study has shown that women with preeclampsia have

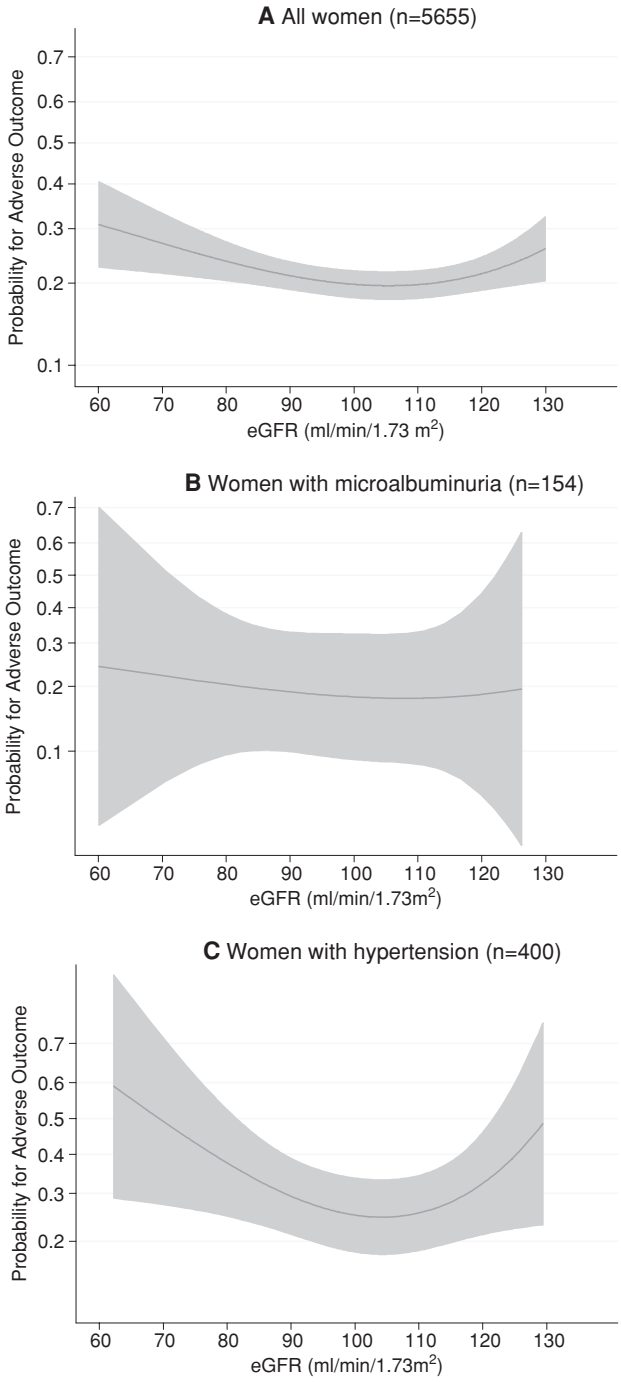


**Fig. 1.** Risk of preeclampsia, small for gestational age or preterm birth by estimated glomerular filtration rate; separate figures for all women (**A**), those with microalbuminuria (**B**) and those with hypertension (**C**). The fractional polynomial model with 95% CI (shaded area) was adjusted for maternal age and parity.

a strongly increased risk of later end-stage renal disease [38].

The strength of this study is a large homogenous population-based sample with a high participation rate. Furthermore, the compulsory personal number given to all Norwegian citizens at birth enabled us to provide information on all subsequent pregnancies. However, several limitations need to be discussed. Kidney function was not measured directly, and although the method used for estimating GFR previously has been found to be unbiased in the present group [5], the accuracy is only moderate, especially for GFR >90 ml/min/1.73 $m^2$ [17]. Urine ACR was only available in a subgroup of the participants and the remaining values were replaced with multiple imputation. There might be some uncertainty associated with the imputation of a large proportion of missing values, but our estimates rely on information from almost 10 000 measured ACR values. Gestational HT and preeclampsia are found to be closely related on diagnosis, and misclassification can therefore not be ruled out. We have chosen to only include cases with preeclampsia in this study. Prevalence estimates should ideally rely on cross-sectional data as the annual decline in eGFR might bias the estimates. We tried to comply with this problem by only using data from women giving birth in the period 1995–97 for estimating the prepregnancy kidney function.

In summary, the prevalence of prepregnancy reduced kidney function in a general population is considerable (18.8%), but the number with moderate to severe impaired kidney function is low (<0.1%). Women with eGFR 60–89 ml/min/1.73 $m^2$ alone or in combination with microalbuminuria were not at increased risk for adverse pregnancy outcomes compared to women with eGFR ≥90 ml/min/1.73 $m^2$, although women with eGFR 60–74 ml/min/1.73 $m^2$ tended to have an increased risk. However, the risk for preeclampsia, SGA or preterm birth increased substantially when those with eGFR 60–89 ml/min/1.73 $m^2$ were also hypertensive.

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