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ORIGINAL ARTICLE

Low birthweight is associated with lower glomerular filtration rate in middle-aged mainly healthy women

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ABSTRACT

Background. Low birthweight (LBW) has been shown to increase the risk of severe kidney disease. Studies have also shown associations between LBW and lower estimated glomerular filtration rate (GFR) in young adults. In this study we investigated whether LBW associates with measured GFR (mGFR) in middle-aged mainly healthy adults.

Methods. We invited individuals with LBW (1100–2300 g) and individuals with normal BW (NBW; 3500–4000 g) ages 41–52 years. GFR was measured using plasma clearance of iohexol. BW and BW for gestational age (BWGA) were obtained from the Medical Birth Registry of Norway and tested as main predictors. GFR was the main outcome.

Results. We included 105 individuals (57 LBW and 48 NBW). The mean GFR was 95 ± 14 mL/min/1.73 m^2 in the LBW group and 100 ± 13 mL/min/1.73 m^2 in the NBW group (P = 0.04). There was a significant sex difference: in women the mean GFR was 90 ± 12 versus 101 ± 14 mL/min/1.73 m^2 in the LBW and NBW groups, respectively (P = 0.006), whereas corresponding values for men were 101 ± 15 versus 100 ± 11 mL/min/1.73 m^2 (P = 0.7). Using linear regression, we found the GFR was 4.5 mL/min/1.73 m^2 higher per 1 kg higher BW for women (P = 0.02), with a non-significant 1.2 mL/min/1.73 m^2 lower GFR for men (P = 0.6). In analyses of BWGA, there was also a significant association for women, but not for men.

Conclusions. Middle-aged mainly healthy women with LBW had lower mGFR as compared with women with NBW. No such difference was found for men.

Keywords: chronic kidney disease, iohexol clearance, low birthweight, measured GFR

INTRODUCTION

Previous studies have shown that low birthweight (LBW) associates with a reduced number of nephrons [1, 2]. This impaired nephron endowment is thought to link BW to an increased risk of kidney disease [3–5]. Supportive of this are several studies showing an increased risk of albuminuria [6–8], reduced kidney function [9–11] and end-stage renal disease [9, 12, 13] for persons with LBW compared with normal BW (NBW), with an overall 1.7 times increase in the risk of kidney-related outcomes [14]. Although the exact mechanism behind this association is unknown, it is believed that the low number of nephrons causes compensatory nephron hypertrophy and hyperfiltration [3]. This, however, comes at a cost of increased strain on the remaining nephrons, leading to increased nephrosclerosis and a further reduction in functional nephron mass [15]. The result is a reduction in glomerular filtration rate (GFR).

In most studies, both in paediatric and adult populations, the GFR is estimated using creatinine-based formulas [16, 17]. This is prone to error, with differences in body composition between individuals with LBW and NBW. We have found only one study using clearance of an external marker [18] and one using urinary creatinine clearance [19]. The use of recollection for BW data [10], inclusion of only patients with a registered BW and exclusion of patients (especially women) who have changed names since birth [9] are other weaknesses of previous studies. In some studies there appears to be a sex difference in the impact of BW on kidney-related outcomes [10, 17]. It is uncertain whether this reflects real differences in the mechanism and effect size of nephron endowment on kidney function or is reflecting errors in creatinine-based GFR estimation.

In this study we aimed to investigate differences in measured GFR (mGFR) in mainly healthy adults ages 40–50 years. We tested BW and BW for gestational age (BWGA) as the main predictors. We also aimed to study possible sex differences.

KEY LEARNING POINTS

What is already known about this subject?

1. Low birthweight (BW) increases the risk of albuminuria, chronic kidney disease and end-stage renal disease.
2. Limited data suggest that there is a sex difference in this association.
3. Except for one twin study and another study after kidney donation, all studies on kidney function in relation to BW have used estimated kidney function rather than measured glomerular filtration rate (mGFR).

What this study adds?

1. This is the first low BW study analysing differences in mGFR in mainly healthy middle-aged adults.
2. Women with low BW had lower mGFR than women with normal BW; there was no difference in men.
3. Both BW and BW for gestational age (GA) is of importance, while GA or preterm versus term seems of less importance.

What impact may this have on practice and policy?

1. This will further acknowledge low BW as a risk factor for kidney disease in adults, even in otherwise healthy middle-aged women.
2. This can guide future research on BW and kidney function, demonstrating the need for using mGFR rather than estimated GFR.

MATERIALS AND METHODS

Registries

Since 1967, the Medical Birth Registry of Norway (MBRN) has registered data on all births in Norway [20]. This compulsory notification includes information about the mother's health before and during pregnancy, as well as data concerning the delivery and the newborn child's health.

Study population

This is a retrospective longitudinal cohort study using BW from the MBRN as the main inclusion source. The MBRN selected 200 participants with LBW and 200 participants with NBW currently residing in one of the five municipalities in the Haugesund area on the west coast of Norway (Haugesund, Karmøy, Bokn, Tysvær and Sveio). The LBW group had a BW of 1100–2300 g and the NBW group had a BW of 3500–4000 g. Participants in both groups were born between 1967 and 1976 and only participants who were the result of a singleton birth were included. Invitations were sent out between May 2018 and April 2019. All non-responders were sent a follow-up letter after ∼1 month, except for the last inclusion group of 60 persons, as enough participants were included. Based on power calculations {90% power, estimated effect size for GFR of 85 versus 95 mL/min/1.73 m^2 [standard deviation (SD) 15] and 5% significance level [8, 14, 17]}, we estimated a need for 48 participants in each group.

Exclusion criteria were diabetes mellitus [defined as either using antidiabetic medications or glycated haemoglobin (HbA1c) >53 mmol/mol (7%)], estimated GFR (eGFR) <50 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration equation [21]), use of antihypertensive medications, regular use of non-steroidal anti-inflammatory drugs (NSAIDs) , cancer (either onset <5 years ago or treated with chemotherapy), allergy to computed tomography contrast agent or known multiple allergies.

Measurements at participation

Participant height was measured and rounded to the nearest centimetre. body weight was measured in kilograms using the same instrument for all participants and one decimal was recorded. Blood pressure was measured seated, once before injection of iohexol and twice during the 30 min following injection. The mean of the last two measurements was used for analysis.

GFR was measured after injection of 5 mL of iohexol (Omnipaque300 mgI/mL, GE Healthcare, Oslo, Norway) via an indwelling intravenous catheter in the antecubital vein of the dominant arm, followed by flushing with 10 mL of normal saline. The syringe and packaging were weighed before and after injection to a precision of 0.01 g. Blood samples were drawn from the opposite arm 2 and 4 h after the injection of iohexol. Analysis of iohexol concentration was done at Haukeland University Hospital. Calculation of GFR was done using the Jødal–Brøchner-Mortensen formula [22].

Urine albumin:creatinine ratio was measured in the first void urine on 3 consecutive days. The median of all three was used for analysis. Microalbuminuria was defined as a median urine albumin:creatinine ratio ≥3 mg/mmol.

Exposure variables

The MBRN provided BW, GA and a z-score of the BWGA by sex (z-score values given as units of SDs from the mean). For use in the analyses, small for GA (SGA) was defined as a z-score

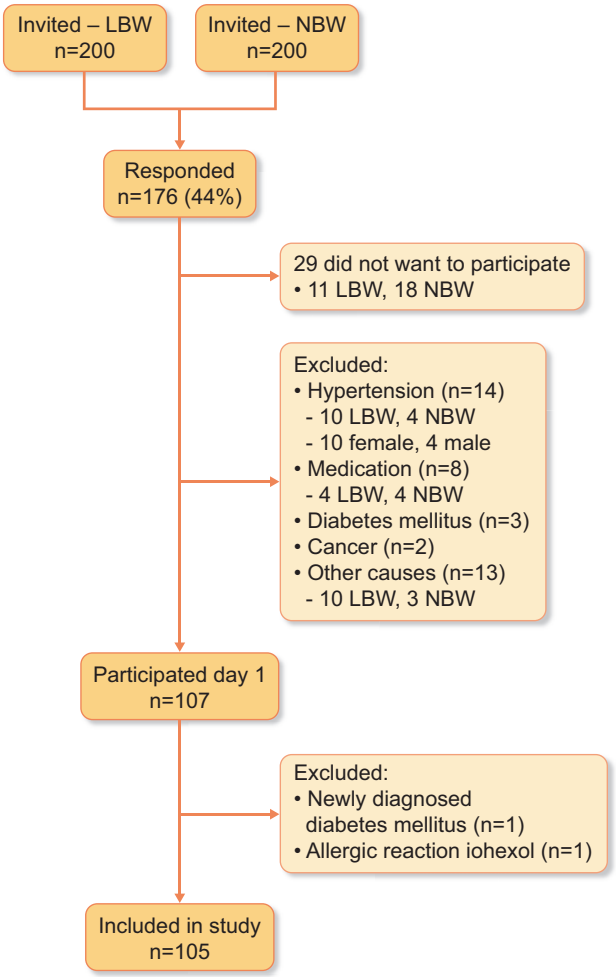

FIGURE 1: Inclusion process. LBW, BW ≤2300 g); NBW, BW 3500–4000 g.

below the 10th percentile, i.e. <−1.28. Maternal age, civil status and information on maternal pre-eclampsia were also obtained from the MBRN. Preterm birth was defined as birth before the 37th week of gestation. Self-reported civil status (living alone or living with spouse/partner), education level (completed higher education or not), household income (above or below 800 000 Norwegian krones (NOK; equivalent to 73 700 euros on 11 March 2020), exercise frequency, smoking status and alcohol consumption were obtained from a questionnaire at examination.

Statistical analyses

All statistics were determined using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) [23]. Descriptive methods were used to characterize. Intergroup differences (LBW versus NBW) were tested using independent *t*-tests for continuous data and chi-squared tests for categorical data, except for maternal pre-eclampsia and maternal civil status, which were analysed with Barnard's unconditional exact test for binomial models [24]. The sex-stratified mean mGFR and 95% confidence interval (CI) was estimated using four different dichotome variables (BW group, z-score of BWGA, preterm birth and maternal pre-eclampsia). The same variables were fitted together with sex and interaction between sex and the main variable in a linear regression model using mGFR as the dependent variable. From this model, the P-value of the sex interaction was reported. We also fitted a sex-stratified multivariate regression model using mGFR as a dependent variable. In this model the independent variables (BW group, BW/kg, z-score of BWGA/1 unit, GA and maternal pre-eclampsia) were tested both unadjusted and adjusted for age at examination, maternal age and maternal civil status. The same modelling was used for a logistic regression model using mGFR <90 mL/min/1.73 m^2 as the dependent variable. A significance level of 0.05 was chosen for all tests.

Ethics

Ethical approval was given by the regional ethics committee (REK2017/927). All participants signed an informed consent formula at inclusion in the study. This study adheres to the Declaration of Helsinki.

RESULTS

Among the 400 people invited, 176 (44%) responded (96 LBW and 80 NBW); 29 did not want to participate and 40 individuals were excluded due to antihypertensive treatment, diabetes, use of various medications or other causes. Two other participants were excluded after Day 1, one due to newly diagnosed diabetes and the other due to possible allergic reaction to iohexol. Details are shown in Figure 1. No information was available for the non-responders and excluded participants. A total of 105 participants (57 LBW and 48 NBW; 45% male) were thus included in the analysis. The group with LBW had a median BW of 2000 g (range 1160–2300) and the NBW group had a median BW of 3735 g (range 3520–3980). Preterm birth was recorded in 68% of the LBW group and none in the NBW group. At examination, there was no significant difference in weight, body mass index (BMI) or body surface area; however, participants with the LBW group seemed to be shorter, with a mean height of 169.7 versus 173.2 cm. This difference was statistically significant for women (mean difference 2.9 cm; P = 0.04) but not for men (mean difference 1.8 cm; P = 0.3). Blood pressure was higher in the LBW group. The median urine albumin:creatinine ratio was 0.4 mg/mmol for both LBW and NBW. Only one participant (male LBW) had a median albumin:creatinine ratio >3 mg/mmol. Three of 54 women that had been pregnant reported pre-eclampsia in their obstetric history (2 LBW and 1 NBW). Table 1 shows detailed characteristics of the two BW groups. Differences in characteristics between male and female participants are shown in Supplementary data, Table S1.

The mean mGFR of participants with LBW was 95 ± 14 mL/min/1.73 m^2, compared with 100 ± 13 mL/min/1.73 m^2 in participants with NBW (P = 0.04). In contrast, the eGFR was not different between the BW groups (P = 0.8; see Table 1 and Supplementary data, Table S1). Comparing the mGFR of participants born SGA compared with appropriate for GA and for participants born preterm versus full term yielded non-significant differences. When analysing men and women separately we found the associations between mGFR and birth-related variables were only seen in women, with no

Table 1. Characteristics of participants at birth and examination

Characteristics	LBW $n = 57$	NBW $n = 48$	P-value
At birth			
Male participants[a]	23 (40)	24 (50)	0.4
BW (g)[b]	2000 (1160–2300)	3740 (3520–3980)	–
BWGA (SD[c])[b]	−1.2 (−4.7–1.8)	0.2 (−0.4–1.5)	<0.001
Premature[a]	39 (70)	0 (0)	<0.001
GA[d]	34.5 ± 3.4	40.3 ± 1.4	<0.001
Maternal pre-eclampsia[e]	8 (14)	1 (2)	0.04
Birth length (cm)[b]	44 (37–49)	51 (48–54)	<0.001
Maternal age (years)[b]	26 (17–43)	25 (18–44)	0.9
Mother living with partner[e]	51 (89)	47 (98)	0.1
Characteristics at examination			
Age (years)[b]	48 (41–52)	46 (41–51)	0.4
Height (cm)[d]	169.7 ± 8.4	173.2 ± 8.0	0.03
Weight (kg)[d]	77.7 ± 18.3	79.0 ± 13.9	0.7
BMI (kg/m^2)[b]	25.9 (17.9–47.3)	25.5 (20.7–41.3)	0.5
Body surface area (m^2)[d]	1.88 ± 0.23	1.93 ± 0.18	0.3
Percentage body fat[d]	30.9 ± 8.99	28.0 ± 9.37	0.1
Systolic blood pressure (mmHg)[d]	126 ± 18	119 ± 11	0.01
Diastolic blood pressure (mmHg)[d]	76 ± 12	70 ± 9	0.004
GFR (mL/min/1.73 m^2)[d]			
eGFR	98 ± 11	99 ± 10	0.8
mGFR	95 ± 14	100 ± 13	0.04
Urine albumin:creatinine ratio (mg/mmol)[b]	0.4 (0–3.2)	0.4 (0–2.6)	0.8
Living with partner[a]	49 (86)	38 (79)	0.5
Completed higher education[a]	29 (51)	19 (40)	0.3
Household income >800 000 NOK[a,f]	34 (60)	30 (62)	0.9
Regular smoker[a]	13 (23)	6 (12)	0.2
Drinking alcohol at least weekly[a]	17 (30)	13 (27)	0.9
Physical exercise at least once a week[a]	41 (73)	39 (81)	0.5

[a]*n* (%), chi-squaredtest.
[b]Median (minimum–maximum), *t*-test.
[c]z-score of BWGA, number of SD from mean.
[d]Mean ± SD, *t*-test.
[e]*n* (%), Barnard's test.
[f]Equivalent to 73 700 euros on 11 March 2020.

Table 2. Sex-stratified mGFR in various subgroups

Variables	Females		Males		Interaction
	Mean (95% CI)	P-value	Mean (95% CI)	P-value	P-value
BW					
LBW	90.4 (86.3–94.5)	0.005	101.4 (95.5–107.4)	0.7	0.03
NBW	100.5 (94.9–106.1)		100.0 (95.5–104.4)		
Zz-score					
SGA	87.3 (81.2–93.3)	0.01	103.6 (95.2–111.9)	0.4	0.02
Not SGA	97.5 (93.2–101.8)		99.9 (95.8–104.0)		
GA					
Preterm	91.8 (86.8–96.9)	0.3	101.9 (94.8–109.0)	0.6	0.3
Term	96.1 (91.0–101.1)		100.0 (95.8–104.2)		
Maternal pre-eclampsia					
Yes	97.8 (86.5–109.0)	0.6	99.9 (85.3–114.5)	0.9	0.7
No	94.3 (90.6–98.1)		100.8 (97.0–104.6)		

For each variable, the sex-stratified means of mGFR (95% CI of the mean) for the two subgroups are shown as mL/min/1.73 m^2. The difference of the mean of the two subgroups was tested using a *t*-test and the P-values are shown. In the total sample, the interaction between the main variables and sex was estimated using a linear regression model and the P-value of the interaction is given.

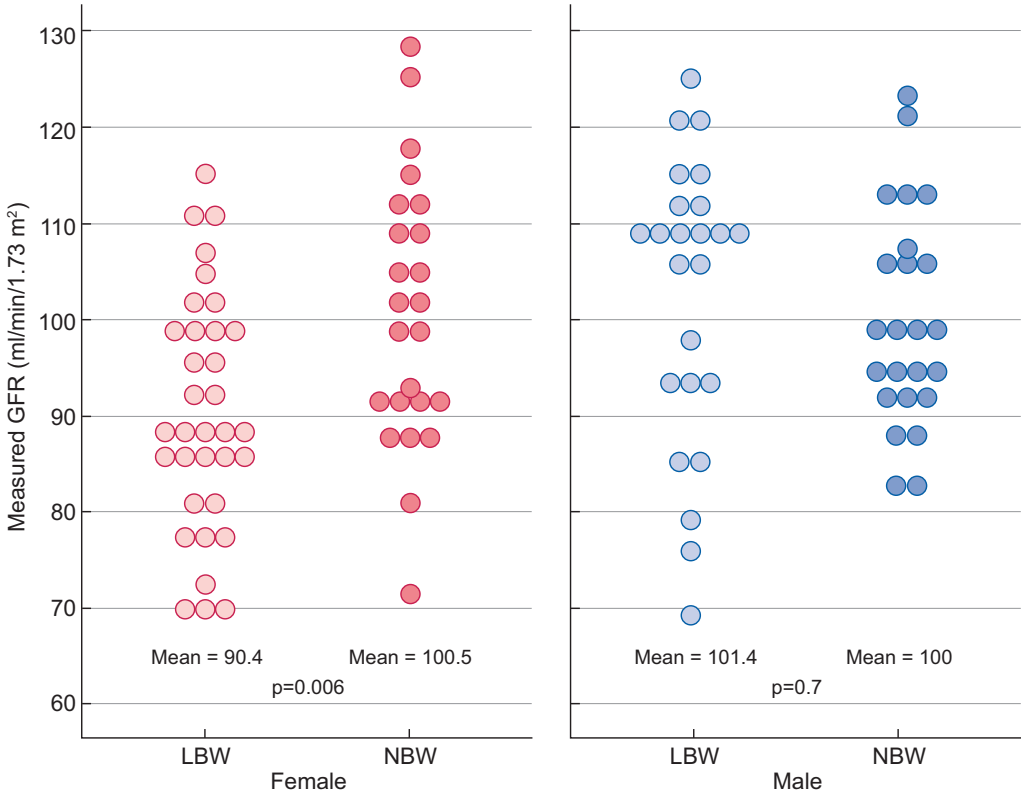

FIGURE 2: mGFR by BW group and sex. LBW, BW ≤2300 g; NBW, BW 3500–4000 g.

Table 3. Multivariate regression analysis with GFR as a dependent variable: sex-stratified results

Variables	Women		Men	
	β (95% CI)	P-value	β (95% CI)	P-value
LBW				
Unadjusted	−10.1 (−17.1 to −3.2)	0.005	1.5 (−6.1 to 9.1)	0.7
Adjusted	−7.7 (−14.5 to −0.8)	0.03	2.8 (−5.2 to 10.7)	0.5
BW per 1 kg				
Unadjusted	6.0 (2.4 to 9.6)	0.002	−0.6 (−4.8 to 3.6)	0.8
Adjusted	4.5 (0.8 to 8.1)	0.02	−1.2 (−5.6 to 3.2)	0.6
z-score per 1 U[a]				
Unadjusted	3.5 (1.0 to 6.0)	0.007	−0.1 (−3.1 to 3.0)	0.9
Adjusted	2.6 (0.1 to 5.1)	0.04	−0.1 (−3.3 to 3.1)	0.9
GA				
Unadjusted	0.8 (−0.2 to 1.8)	0.1	0.0 (−1.0 to 0.9)	0.9
Adjusted	0.5 (−0.5 to 1.4)	0.3	−0.2 (−1.2 to 0.8)	0.7
Maternal pre-eclampsia				
Unadjusted	−3.4 (−17.8 to 11.0)	0.6	0.9 (−11.5 to 13.2)	0.9
Adjusted	−3.9 (−17.2 to 9.4)	0.6	1.3 (−11.2 to 13.8)	0.8

Adjustment for possible confounders: age at examination, maternal age and maternal civil status.
[a]Sex specific z-score of BWGA, 1 U equals 1 SD.

significant differences for men. In Table 2, sex-stratified mGFR differences are shown. For women, both BW groups and BWGA gave significant results. We further tested the effects using regression statistics demonstrating a significant interaction with sex, therefore subsequent analyses were sex stratified. Figure 2 shows the distribution of mGFR for men and women in the two groups.

Associations were further tested using linear regression statistics with mGFR as the dependent variable. For women, having LBW was associated with 10.1 mL/min/1.73 m^2 lower mGFR (P = 0.005; see Table 3). When adjusting for age at examination, maternal age and maternal civil status, the difference was 7.7 mL/min/1.73 m^2 (P = 0.03). For men, no significant associations were seen. Similarly, a 1 kg higher BW was associated with a 6.0 mL/min/1.73 m^2 higher mGFR for women (P = 0.002) but no significant difference for men. For z-score, a 1 unit higher z-score (defined as 1 SD higher BWGA in the MBRN) associated with an mGFR of 3.5 mL/min/1.73 m^2 higher for women. Again,

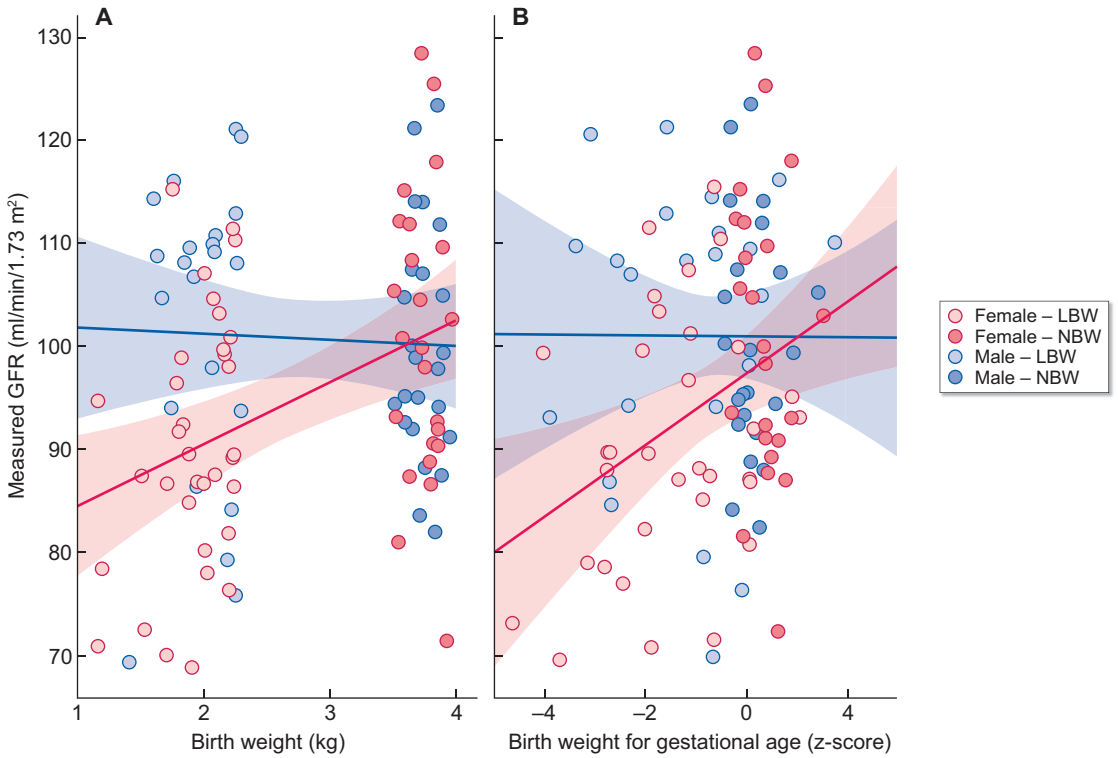

FIGURE 3: mGFR by BW and z-score. LBW, BW ≤2300 g; NBW, BW 3500–4000 g.

Table 4. Logistic regression model for low GFR

Variables	Women		Men	
	β (95% CI)	P-value	β (95% CI)	P-value
LBW				
Unadjusted	4.8 (1.5–15.9)	0.01	1.4 (0.3–6.0)	0.7
Adjusted	3.8 (1.1–13.5)	0.04	1.1 (0.2–5.8)	0.9
BW (kg)				
Unadjusted	0.4 (0.2–0.8)	0.008	0.9 (0.4–2.0)	0.8
Adjusted	0.5 (0.2–0.9)	0.03	1.0 (0.4–2.5)	1
z-score				
Unadjusted	0.5 (0.3–0.8)	0.007	0.9 (0.5–1.5)	0.6
Adjusted	0.5 (0.3–0.9)	0.01	0.7 (0.3–1.6)	0.5
GA				
Unadjusted	0.9 (0.8–1.0)	0.2	1.0 (0.8–1.2)	0.9
Adjusted	0.9 (0.8–1.1)	0.5	1.0 (0.8–1.3)	0.7
Maternal pre-eclampsia				
Unadjusted	0.7 (0.1–5.3)	0.7	0.3 (0.0–2.1)	0.2
Adjusted	0.8 (0.1–6.5)	0.8	0.3 (0.0–3.8)	0.4

Sex-stratified analysis showing OR (95% CI) for GFR <90 mL/min/1.73 m^2.

no difference was found for the men. Figure 3 shows these associations graphically for BW and BWGA (z-score).

We defined normal mGFR as >90 mL/min/1.73 m^2 and using logistic regression statistics we analysed the odds ratio (OR) for having mGFR <90 mL/min/1.73 m^2. This in accordance with the GFR cut-off used in chronic kidney disease (CKD) definitions [25] (no participants had GFR <60 mL/min/1.73 m^2). In women, LBW was associated with an unadjusted OR of 4.8 (95% CI 1.5–16; P = 0.01) for having a GFR <90 mL/min/1.73 m^2 (Table 4). In men, the corresponding unadjusted OR was 1.4 (95% CI 0.3–6.0; P = 0.7). Adjusted analyses showed similar results.

DISCUSSION

This study is, to our knowledge, the first study to investigate whether external marker–based mGFR associates with BW in middle-aged mainly healthy adults. The study shows that mainly healthy women with LBW have lower mGFR than women with NBW and also that these associations are significant for BWGA. Surprisingly, no significant associations were found for men. The study sample comprised a fairly healthy population without diabetes or the use of antihypertensive medication, and the NBW group had lower blood pressure and similar or lower BMI than the age-adjusted general population [26, 27].

The findings of lower mGFR for women with LBW are in accordance with other studies showing associations between BW and kidney function [14, 28]. Two previous studies have used mGFR to study the association between BW and kidney function: Berglund *et al.* [18] studied previous kidney donors. They found that higher BW reduced the risk of albuminuria, while there was no association between BW and risk of mGFR <60 mL/min/1.73 m^2. However, only 15 of 216 participants had a BW <2500 g, and it should be remembered that these participants had undergone nephrectomy, an operation that leads to greater changes in GFR than would be expected for BW. Gielen *et al.* [19] studied twins using creatinine clearance and found that a 1 kg higher BW was associated with a 6 mL/min higher creatinine clearance. In a meta-analysis by Das *et al.* [28], the effect on GFR of 1 kg higher BW was found to be 2.09 mL/min/1.73 m^2. However, this meta-analysis included

studies of all age groups and several studies on children. In our study, the overall effect on GFR per 1 kg higher BW was 3.45 mL/min/1.73 m^2. For women, the effect was 4.5 mL/min/1.73 m^2 after adjustments for age at examination, maternal age and civil status. The analysis of association between BWGA and mGFR yielded a similar significant association for women, but not for men. In a Swedish registry study, GA was found to be associated with the risk of CKD [29]. However, this effect was attenuated in older age, which could explain why we did not find the same association, as the most diseased people are already excluded.

Most previous studies suggest a stronger effect of BW on kidney disease and eGFR in men than in women [9–11, 17, 30]. We also showed a significant sex difference. However, in our study the association between BW and GFR was only present in women. This could have several explanations. First, in contrast to other studies, we used external marker–based mGFR instead of eGFR or creatinine clearance, giving GFR values not biased by muscle mass etc., better representing the true GFR. Second, we excluded patients with diabetes, treatment for hypertension and/or eGFR <50 mL/min/1.73 m^2 and have therefore probably excluded those with the strongest association between BW and low GFR. If LBW associates with kidney function mainly indirectly via increased risk of traditional risk factors such as hypertension, diabetes and metabolic syndrome [31], then the effect of this could be even more important and there could be significant sex differences. Third, there could be sex differences in the mechanisms of kidney adaption and early kidney damage to being born with a small number of nephrons. As global GFR is the sum of the filtration in all nephrons, it is difficult to distinguish normal filtration in a normal number of nephrons from that of hyperfiltration in a reduced number of nephrons. It can be speculated that a sex difference in age-related hyperfiltration and adaption to nephron loss may exist, as suggested by other researchers [15, 32, 33]. More studies are needed to explore the natural course of GFR changes in adult age and whether this is affected by BW. Such studies should probably include a cross section of the total population, both healthy and unhealthy persons, and also including ages >50 years.

The strength of this study is that a compulsory national registry was used for extraction of data on BW and other perinatal variables. The Norwegian population registry allowed for the detection of all eligible participants with the given characteristics living in our local area and we could thus include subjects within a certain age group that were the result of a singleton birth. The use of mGFR rather than eGFR is a novelty in BW-related GFR research, improving the validity of our results. In fact, eGFR would not be sufficient to show the difference between the two BW groups in our material. Compared with general population data, we observed that our study group with NBW seemed to have lower blood pressure and BMI and thus seemed to comprise a very healthy group of subjects. By studying a fairly healthy population, our results reflect the association between BW and kidney function, independent of several other possible confounders. On the other hand, we have probably also excluded patients who had low GFR mainly due to LBW. In addition, the most severe LBW patients who might have severe CKD may die at an early age. The main limitation is the low final participation rate of the individuals includable in the study. In the original power calculation we estimated the need for 48 persons in each group. This was fulfilled in the total sample (57 LBW and 48 NBW). However, with the need for sex-stratified analysis, the groups are smaller. Especially for the men, where the differences were smaller, this study may have been underpowered. The project was time consuming for the participants and this may have caused selection bias. The study only included Norwegians and may not reflect associations in other populations.

In conclusion, our study shows that mGFR in mainly healthy women 40–50 years of age is associated with BW. The association, which was only demonstrated in women, could be explained by underlying sex-specific mechanisms that should be investigated further.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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