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Effect of intrauterine growth restriction on kidney function at young adult age: the Nord Trøndelag Health (HUNT 2) Study

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Abstract

Background

The hypothesis of intrauterine origin of adult disease is debated. We tested whether intrauterine growth restriction is associated with later kidney function.

Study design

Prospective cohort study.

Setting and participants

7,457 Norwegian adults aged 20 to 30 years participating in the population based Nord Trøndelag Health Study (1995-1997) with data for birth weight, gestational age, and maternal and perinatal risk factors registered at the Medical Birth Registry of Norway.

Predictor

Birth weight expressed as an SD score (SDS) to adjust for gestational age and sex. Subjects with a birth weight SDS less than -2.0, -2.0 to -1.3, and -1.3 to 1.3 were defined as very small, small, and appropriate for gestational age, corresponding to less than the 3rd, 3rd to 10th, and 10th to 90th percentiles, respectively.

Outcome and measurements

Kidney function estimated using the Cockcroft-Gault and isotope dilution mass spectrometry-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. Values less than the sex-specific 10th percentile were defined as low-normal kidney function.

Results

Compared with men with birth weight appropriate for gestational age ($n = 2,755$), odds ratios for low-normal creatinine clearance (<100 mL/min) were 1.66 (95% confidence interval [CI], 1.16 to 2.37) if small for gestational age ($n = 261$) and 2.40 (95% CI, 1.46 to 3.94) if very small for gestational age ($n = 101$). Kidney function estimated using the MDRD Study equation gave similar results. Women ($n = 3,126, 283, \text{ and } 112$, respectively) had odds ratios of 1.65 (95% CI, 1.17 to 2.35) and 2.00 (95% CI, 1.21 to 3.29) for low-normal creatinine clearance (<80 mL/min), whereas the association was not significant using the MDRD Study equation. Using linear regression, creatinine clearance decreased by 4.0 mL/min (95% CI, 3.3 to 4.6) in men and 2.9 mL/min (95% CI, 2.2 to 3.5) in women per 1-SDS decrease. Adjusting for possible confounders did not influence results.

Limitations

Selection bias could be a problem because the participation rate was 49%, but there were no statistically significant differences between participants and nonparticipants regarding maternal and perinatal characteristics. Adjusting kidney function for body size can be a special problem in people with intrauterine growth restriction.

Conclusions

Although effects were still small in young adulthood, intrauterine growth restriction was significantly associated with low-normal kidney function. The effect was weaker and less consistent in women compared with men.

Introduction

Intrauterine growth restriction (IUGR) is increasingly proposed as a mechanism in the pathogenesis of cardiovascular disease. An increased risk of hypertension,¹ subclinical atherosclerosis assessed by using carotid intima-media thickness measurement,² nonfatal cardiovascular events³ and cardiovascular death⁴ were found in persons with low birth weight (BW). A few studies suggested that the propensity to chronic kidney disease may also be established in utero, and Brenner and Chertow⁵ were the first to postulate that IUGR may cause a decreased number of nephrons, leading to hypertension and reduced kidney function.

Low kidney volume and nephron number were observed after IUGR in several animal models^{6,7} and also in humans, newborns as well as adults, who died of nonrenal causes.⁸⁻¹⁰ The clinical consequences of these alterations were investigated at different levels, and associations were found of IUGR with microalbuminuria,^{11,12} faster progression of renal dysfunction in patients with specific kidney diseases,^{13,14} and end-stage renal disease (ESRD).^{15,16} Because IUGR also was associated with other diseases, such as type 2 diabetes mellitus, it is difficult to disentangle direct from indirect effects of IUGR on advanced renal failure. For that reason, follow-up studies of younger populations are necessary. A relationship between IUGR and renal function at 19 years of age was found in a prospective cohort study of subjects born very premature,¹⁷ however, to date, no cohort study investigated the effect of IUGR on young adult kidney function in a general population.

We describe results from a large unselected cohort aged 20 to 30 years in which we assessed the relationship between BW (adjusted for sex and gestational age) and later kidney function to test the hypothesis that IUGR itself is primarily responsible for impaired kidney function. Because of the close relationship between kidney function and blood pressure, we also used blood pressure as a secondary outcome.

Methods

Population

The Health Survey of Nord-Trøndelag (HUNT 2 Study) is a general health survey conducted in 1995-1997 in Nord-Trøndelag County, Norway, with a population of 127,000. All residents of this stable and homogeneous population (97% whites) aged 20 years and older were invited for the survey. Objectives, methods, and participation in the HUNT 2 Study are described in detail elsewhere.¹⁸ The present study also used data from the national Medical Birth Registry. Since 1967, midwives or attending physicians have been obliged to forward medical data for

each childbirth to the Medical Birth Registry.¹⁹ Because all liveborns are assigned a unique identification number, linkage between databases is possible in Norway. The present study is based on an anonymized version of this record linkage and comprised a subgroup of the HUNT 2 Study, i.e., subjects born between 1967 and 1977. All participants gave written informed consent, and the study was approved by the Regional Committee for Medical Research Ethics, the National Data Inspectorate, and the Directorate of Health and Social Affairs. Chronic kidney disease has a high prevalence in Norway, as well as in other western countries (10%).²⁰ ESRD incidence is low (99 cases/million inhabitants per year), and the most frequent causes are hypertension (29%), glomerulonephritis (18%), and diabetes (15%).²¹

Measurements

More than 99% of pregnant women in Norway receive standardized antenatal care.²² Recording of live births is 100% complete in Norway. BW was recorded to the nearest 10 g, and gestational age was based on the last menstrual period. Data for congenital malformations, pregnancy complications, and maternal conditions were also recorded. Diagnostic criteria for preeclampsia fulfilled the 1972 recommendations of the American College of Obstetricians and Gynecologists, which defined preeclampsia as increased blood pressure ($\geq 140/90$ mm Hg) after 20 weeks of gestation together with proteinuria, edema, or both.

Relevant data at a young adult age were obtained as part of the HUNT 2 Study: medical history, risk factors, education, and family history of cardiovascular disease. Height was measured to the nearest 1.0 cm, and weight, to the nearest 0.5 kg, with participants lightly clothed without wearing shoes. Blood pressure was measured by specially trained nurses or technicians using a Dinamap 845 XT (Critikon, Tampa, FL) based on oscillometry. Cuff size was adjusted after measuring arm circumference. Blood pressure measurements were performed after the participant had been seated for at least 2 minutes with the cuff around the arm with the arm resting on a table. Blood pressure was measured automatically 3 times at 1-minute intervals. For all analyses, mean values of the second and third systolic and diastolic measurements were obtained. Fresh serum samples were analyzed within 2 days on a Hitachi 911 Autoanalyzer (Hitachi, Mito, Japan), applying reagents from Roche (Roche Diagnostics, Mannheim, Germany). Serum creatinine was measured by using a blank-rate Jaffé method.

Statistical Analysis

Subjects with congenital malformations and women pregnant at the time of assessment were not eligible for inclusion because of possible influences on body composition and renal function. There is controversy about how to index kidney function for body size.²³ Therefore, we used different estimates of kidney function. Creatinine clearance was estimated using the Cockcroft-Gault formula, and glomerular filtration rate (GFR) was estimated using the isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal

Disease (MDRD) Study equation. Results are presented as not adjusted for body surface area (in milliliters per minute) and adjusted for body surface area (in milliliters per minute per 1.73 m²) for both equations.^{24,25}

Creatinine clearance (mL/min)

$$= (140 - \text{age}) / (\text{serum creatinine}[\text{mg/dL}] \times (\text{weight}[\text{kg}] / 72 \times 0.85 \text{ if female}))$$

GFR (mL/min / 1.73m²)

$$= 175 \times \text{serum creatinine (mg/dL)} - 1.154 \times \text{age} - 0.203 \times (\text{0.742 if female})$$

For the MDRD Study equation, now designed for use with IDMS-traceable serum creatinine values to avoid problems with interlaboratory calibration differences, we recalibrated our original Jaffè-based creatinine values to the Roche enzymatic method.²⁶

To reflect intrauterine growth, we expressed BW as an SD score (BW-SDS) to correct for gestational age and sex by using Scandinavian references.²⁷ Very small for gestational age (VSGA) was defined as a BW less than the 3rd percentile for gestational age (< -2.0 SDS); small for gestational age (SGA), as a birth weight between the 3rd and 10th percentile (-2.0 to -1.3 SDS); and appropriate for gestational age (AGA), as a birth weight between the 10th and 90th percentile (-1.3 to 1.3 SDS). Similar categories were used for BW (2,450, 2,870, and 4,190 g, respectively) and gestational age (36, 38, and 42 weeks, respectively). We used low-normal kidney function, defined as values less than the sex-specific 10th percentile, as our primary outcome. Blood pressure was a secondary outcome.

Based on the Medical Birth Registry, we compared obstetric and neonatal characteristics of HUNT 2 participants and nonparticipants by using 2-sample *t*-test or Mann-Whitney *U* test, when appropriate. Nonlinear associations in our study population were then tested for by categorizing BWSDS, BW, and gestational age, and age-adjusted logistic regression analysis was used to assess the effect of IUGR. Linear regression was used if appropriate to assess the effect of IUGR as a continuous variable. Blood pressure was analyzed as a continuous variable. All analyses were performed separately for men and women,²³ and analyses were repeated with adjustment for maternal risk factors (age, preexisting diabetes and/or kidney disease, and preeclampsia), adult smoking, and educational level.

Results

Forty-nine percent of all adults in Nord-Trøndelag County born between 1967 and 1977 participated in the HUNT 2 Study (n = 8,666). BW-SDS was missing for 490 participants, and

133 participants had improbable values BW-SDS < -5 or > 5), leaving 8,043 subjects eligible. As listed in Table 1, based on the Medical Birth Registry, there were no significant differences in BWs or other obstetric, neonatal, and maternal characteristics between study subjects and nonparticipants in Nord-Trøndelag County. The proportion of males was significantly lower among participants. Persons with congenital malformations (n = 126) and women pregnant at the time of the study (n = 323) were excluded, and 137 had missing data for serum creatinine or weight needed for estimating kidney function. Therefore, data from 7,457 subjects (3,534 males and 3,923 females) were analyzed. BWs ranged from 1,020 to 5,630 g, comprising 213 VSGA subjects, 544 SGA subjects, 5,881 AGA subjects, and 819 large-for-gestational-age subjects. Mean BWs in these groups were $2,448 \pm 311$ (SD), $2,851 \pm 253$, $3,499 \pm 411$, and $4,321 \pm 391$ g, respectively. Table 2 lists characteristics of the study groups at the time of the HUNT 2 examination.

Table 1. Demographic, obstetric, and neonatal characteristics of all subjects born 1967-1977 in Nord-Trøndelag county, Norway

	Participants in HUNT 2 Study (n = 8043)	Nonparticipants (n = 8499)	P
Men (%)	45.4	59.0	<0.001
Dead after HUNT 2 (%)	0.5	0.7	0.04
Maternal hypertension (%)	0.1	0.1	0.9
Maternal chronic kidney disease (%)	0.7	0.8	0.4
Maternal diabetes mellitus (%)	0.1	0.1	0.9
Pregnancy-induced hypertension (%)	1.3	1.2	0.9
Preeclampsia (%)	4.6	4.5	0.8
Obstetric complications (%)	21.9	23.0	0.09
Gestational age (wk)	39.9 ± 1.8	39.9 ± 1.9	0.9
BW (g)	$3,510 \pm 539$	$3,515 \pm 535$	0.5
BW < 2,500 g (%)	3.4	3.4	0.9
BW > 4,000 g (%)	16.2	16.4	0.8
BW-SDS	0.02 ± 1.08	-0.01 ± 1.08	0.2
BW-SDS -2.0 to -1.3 (SGA) (%)	7.2	7.5	0.4
BW-SDS < -2.0 (VSGA) (%)	2.9	3.3	0.1

Note: Values expressed as mean \pm SD or percent. Binary variables compared by using chi-square test, continuous variables compared by using 2-sample *t*-test. Subjects born SGA and VSGA were defined by using BW-SDSs to also account for gestational age and sex.

Abbreviations: HUNT 2, Nord Trøndelag Health Study; BW, birth weight; SDS, SD score; SGA, small for gestational age; VSGA, very small for gestational age.

Table 2. Characteristics of HUNT 2 participants examined 1995-1997 by category of intrauterine growth

	VSGA (n = 213)	SGA (n = 544)	AGA (n = 5881)	P
Age (y)	24.4 ± 2.8	24.7 ± 2.9	24.7 ± 2.9	0.1
Men (%)	47.4	48.0	46.8	0.7
Low education* (%)	48.3	47.7	44.4	0.08
Height (cm)	169.4 ± 9.2	170.2 ± 8.5	173.0 ± 8.9	<0.001
Weight (kg)	70.0 ± 13.9	71.4 ± 13.5	74.2 ± 14.1	<0.001
Body surface area (m ²)	1.80 ± 0.20	1.82 ± 0.19	1.87 ± 0.20	<0.001
Body mass index (kg/m ²)	24.3 ± 4.0	24.6 ± 4.0	24.7 ± 3.9	0.3
Family history of DM or CVD (%)	33.8	27.0	27.6	0.2
Physical inactivity† (%)	13.5	13.1	13.6	0.8
Current smoking (%)	35.2	29.4	28.0	0.04
Diabetes (%)	0.9	0.9	0.5	0.2
Antihypertensive treatment (%)	0.0	0.2	0.4	0.3
Systolic blood pressure (mm Hg)	128.7 ± 12.7	127.4 ± 13.8	126.2 ± 13.1	<0.01
Diastolic blood pressure (mm Hg)	73.1 ± 9.0	71.7 ± 8.6	71.2 ± 8.6	<0.01

Note: Variables presented as mean ± SD or percentage. VSGA birth weight adjusted for gestational age and sex less than 3rd percentile, SGA birth weight adjusted for gestational age and sex between 3rd and 10th percentiles, and AGA birth weight adjusted for gestational age and sex between 10th and 90th percentiles. Binary variables compared by using the linear-by-linear test for trend in a 2 × 3 cross-table; continuous variables compared using 1-way analysis of variance.

Abbreviations: HUNT 2, Nord Trøndelag Health Study; SGA, small for gestational age; VSGA, very small for gestational age; AGA, appropriate for gestational age; DM, diabetes mellitus; CVD, cardiovascular disease (i.e. cerebral stroke or myocardial infarction age < 60 years).

* Less than 12 years.

† Less than 1 hour per week of light physical activity.

Table 3. Odds Ratios for low-normal kidney function estimated using different methods at a young adult age by intrauterine growth observed in HUNT 2 participants born 1967-1976

Intrauterine growth	Men					Women				
	Cockcroft-Gault* (mL/min)	Cockcroft-Gault† (mL/min/1.73 m ²)	MDRD Study Equation‡ (mL/min)	MDRD Study Equation§ (mL/min/1.73 m ²)	Cockcroft-Gault† (mL/min/1.73 m ²)	Cockcroft-Gault* (mL/min)	Cockcroft-Gault† (mL/min/1.73 m ²)	MDRD Study Equation‡ (mL/min)	MDRD Study Equation§ (mL/min/1.73 m ²)	
Birth weight										
<3rd percentile (<2,450 g)	2.42 (1.43-4.08)	2.00 (1.15-3.49)	2.70 (1.61-4.51)	2.68 (1.58-4.51)	1.40 (0.80-2.44)	0.89 (0.45-1.72)	1.07 (0.58-1.97)	1.01 (0.54-1.90)		
3rd-10th percentile (2,450-2,870 g)	1.80 (1.20-2.69)	1.43 (0.92-2.21)	1.52 (0.99-2.34)	1.19 (0.73-1.92)	1.61 (1.14-2.29)	1.33 (0.92-1.94)	1.24 (0.85-1.82)	1.19 (0.81-1.77)		
10th-90th percentile (2,870-4,190 g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Multiaadjusted birth weight										
<3rd percentile (<2,450 g)	2.43 (1.39-4.25)	1.86 (1.00-3.44)	2.21 (1.23-3.96)	2.35 (1.30-4.24)	1.71 (0.97-3.01)	1.07 (0.55-2.09)	1.19 (0.62-2.25)	1.08 (0.55-2.11)		
3rd-10th percentile (2,450-2,870 g)	1.84 (1.21-2.80)	1.51 (0.95-2.40)	1.41 (0.88-2.25)	1.06 (0.62-1.82)	1.84 (1.28-2.64)	1.50 (1.01-2.20)	1.31 (0.87-1.96)	1.23 (0.81-1.86)		
10th-90th percentile (2,870-4,190 g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Gestational age										
<3rd percentile (<36 wk)	1.81 (1.02-3.20)	1.99 (1.14-3.48)	2.17 (1.26-3.75)	1.60 (0.87-2.94)	1.25 (0.64-2.46)	0.72 (0.31-1.66)	0.99 (0.47-2.09)	0.62 (0.25-1.55)		
3rd-10th percentile (36-38 wk)	1.22 (0.80-1.85)	1.00 (0.64-1.56)	1.06 (0.68-1.65)	1.03 (0.66-1.63)	0.95 (0.60-1.52)	1.11 (0.71-1.73)	1.08 (0.69-1.70)	1.40 (0.92-2.12)		
10th-90th percentile (38-42 wk)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Multiaadjusted gestational age										
<3rd percentile (<36 wk)	1.75 (0.97-3.17)	1.83 (1.01-3.31)	2.00 (1.12-3.56)	1.41 (0.73-2.73)	1.17 (0.57-2.37)	0.61 (0.24-1.52)	0.74 (0.32-1.73)	0.50 (0.18-1.38)		
3rd-10th percentile (36-38 wk)	1.20 (0.78-1.87)	0.94 (0.57-1.54)	0.99 (0.61-1.60)	1.04 (0.64-1.68)	1.08 (0.67-1.74)	1.21 (0.76-1.90)	1.11 (0.69-1.77)	1.39 (0.89-2.17)		
10th-90th percentile (38-42 wk)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Birth weight by gestational age										
<3rd percentile (<-2.0 SDS)	2.40 (1.46-3.94)	1.90 (1.11-3.25)	2.74 (1.68-4.48)	2.10 (1.22-3.60)	2.00 (1.21-3.29)	1.08 (0.58-1.99)	1.07 (0.58-1.98)	0.99 (0.52-1.85)		

Table 3. (continued)

Intrauterine growth	Men					Women				
	Cockcroft-Gault* (mL/min)	Cockcroft-Gault† (mL/min/1.73 m ²)	MDRD Study Equation‡ (mL/min)	MDRD Study Equation§ (mL/min/1.73 m ²)	MDRD Study Equation¶ (mL/min)	Cockcroft-Gault* (mL/min)	Cockcroft-Gault† (mL/min/1.73 m ²)	MDRD Study Equation‡ (mL/min)	MDRD Study Equation§ (mL/min/1.73 m ²)	MDRD Study Equation¶ (mL/min)
3rd-10th percentile (-2 to -1.3 SDS)	1.66 (1.16-2.37)	1.19 (0.80-1.78)	1.65 (1.14-2.39)	1.50 (1.02-2.19)	1.54 (1.08-2.19)	1.21 (0.83-1.77)	1.17 (0.80-1.71)	1.21 (0.83-1.77)	0.90 (0.59-1.37)	1.00
10th-90th percentile (-1.3 to 1.3 SDS)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Multiadjusted birth weight by gestational age										
<3rd percentile (<-2.0 SDS)	2.67 (1.59-4.48)	2.04 (1.14-3.63)	2.22 (1.26-3.89)	1.70 (0.90-3.20)	2.44 (1.46-4.07)	1.29 (0.69-2.39)	1.34 (0.72-2.48)	1.29 (0.69-2.39)	1.20 (0.63-2.28)	1.00
3rd-10th percentile (-2 to -1.3 SDS)	1.63 (1.11-2.39)	1.22 (0.80-1.87)	1.72 (1.16-2.52)	1.62 (1.09-2.43)	1.46 (1.00-2.14)	1.19 (0.79-1.78)	1.19 (0.79-1.79)	1.19 (0.79-1.79)	0.87 (0.55-1.37)	1.00
10th-90th percentile (-1.3 to 1.3 SDS)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Note: Values expressed as odds ratio (95% confidence interval). Age-adjusted logistic regression analysis on the effect of categories of birth weight, gestational age, and birth weight by gestational age on kidney function. Kidney function was estimated by using different methods, and low-normal kidney function was defined as values less than the sex-specific 10th percentile with cutoff values as noted. Regression analyses were also adjusted for maternal risk factors (age, diabetes, kidney disease, and preeclampsia) and potential confounders at adult age (smoking and education). To convert creatinine clearance in mL/min to mL/s, multiply by 0.01667; glomerular filtration rate in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667. Abbreviations: HUNT, Nord Trøndelag Health; SDS, SD score; MDRD, Modification of Diet in Renal Disease.

* Cutoff value: 101 mL/min in men and 80 mL/min in women.

† Cutoff value: 92 mL/min/1.73 m² in men and 85 mL/min/1.73 m² in women.

‡ Cutoff value: 104 mL/min in men and 86 mL/min in women.

§ Cutoff value: 92 mL/min/1.73 m² in men and 86 mL/min/1.73 m² in women.

Table 4. Association between kidney function estimated using different methods at a young adult age and intrauterine growth observed in HUNT 2 participants born 1967-1976

Intrauterine Growth	Men						Women					
	Cockcroft-Gault (mL/min)	Cockcroft-Gault (mL/min/1.73 m ²)	MDRD Study Equation (mL/min)	MDRD Study Equation (mL/min/1.73 m ²)	Cockcroft-Gault (mL/min)	Cockcroft-Gault (mL/min/1.73 m ²)	MDRD Study Equation (mL/min)	MDRD Study Equation (mL/min/1.73 m ²)	Cockcroft-Gault (mL/min)	Cockcroft-Gault (mL/min/1.73 m ²)	MDRD Study Equation (mL/min)	MDRD Study Equation (mL/min/1.73 m ²)
Birth weight (1 kg)												
Age adjusted	7.3 (6.0-8.6)	2.8 (2.0-3.6)	6.1 (4.8-7.4)	1.7 (0.6-2.7)	5.5 (4.2-6.8)	1.8 (1.0-2.7)	3.8 (2.5-5.1)	-0.1 (-1.3-1.1)				
Multiadjusted	7.2 (5.8-8.6)	2.6 (1.8-3.4)	5.5 (4.1-6.9)	1.0 (-0.1-2.1)	5.7 (4.3-7.0)	2.0 (1.1-2.9)	3.9 (2.5-5.2)	0.0 (-1.2-1.2)				
Gestational age (1 wk)												
Age adjusted	0.3 (-0.1-0.7)	0.2 (-0.1-0.4)	0.3 (-0.1-0.7)	0.2 (-0.2-0.5)	0.2 (-0.2-0.6)	0.1 (-0.1-0.4)	0.2 (-0.2-0.6)	0.2 (-0.2-0.5)				
Multiadjusted	0.2 (-0.2-0.6)	0.1 (-0.1-0.4)	0.2 (-0.2-0.7)	0.2 (-0.2-0.5)	0.1 (-0.3-0.5)	0.1 (-0.1-0.4)	0.2 (-0.2-0.6)	0.2 (-0.2-0.6)				
Birth weight by gestational age (1 SDS)												
Age adjusted	4.0 (3.3-4.6)	1.5 (1.1-1.9)	3.2 (2.6-3.9)	0.8 (0.3-1.3)	2.9 (2.2-3.5)	0.9 (0.5-1.3)	1.9 (1.3-2.6)	-0.1 (-0.7-0.5)				
Multiadjusted	4.0 (3.3-4.7)	1.4 (1.0-1.8)	3.0 (2.3-3.7)	0.4 (-0.2-1.0)	3.1 (2.4-3.7)	1.0 (0.6-1.5)	2.0 (1.4-2.7)	-0.1 (-0.7-0.5)				

Note: The effect (95% confidence interval) of intrauterine growth on kidney function was first adjusted for subject age in a linear regression analysis. In the multiadjusted analysis, we also adjusted for maternal risk factors (age, diabetes, kidney disease, and preeclampsia) and potential confounders at adult age (smoking and education). To convert creatinine clearance in mL/min to mL/s, multiply by 0.01667; glomerular filtration rate in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

Abbreviations: HUNT 2, Nord Trøndelag Health; SDS, standard deviation score; MDRD, Modification of Diet in Renal Disease.

Table 3 lists risks for low-normal kidney function, defined as estimates less than the 10th percentile, for different categories of BW, gestational age, and BW by gestational age. In men, crude BW less than the 3rd percentile (< 2,450 g) was associated with at least a 2 times greater risk of low-normal kidney function independent of how kidney function was estimated. Similar results were found for those born with a gestational age less than 36 weeks. When assessing intrauterine growth as BW adjusted for gestational age, we found that those born SGA (3rd to 10th percentile) also had significantly increased risk. Defining low-normal kidney function as Cockcroft-Gault estimates less than 100 mL/min (< 1.67 mL/s), men born VSGA (< 3rd percentile) had an odds ratio (OR) of 2.40 (95% confidence interval [CI], 1.46 to 3.94) compared with those born appropriate for gestational age. Men born SGA (3rd to 10th percentile) had an OR of 1.66 (95% CI, 1.16 to 2.37) for low-normal kidney function. A significant trend for increasing risk with decreasing BW-SDS scores was found ($P < 0.001$). In women, the association with IUGR was much less consistent and highly dependent on how kidney function was estimated. Defining low-normal kidney function as Cockcroft-Gault estimates less than 80 mL/min (< 1.33 mL/s), a significant association was found with BW adjusted for gestational age for women born VSGA (OR, 2.00; 95% CI, 1.21 to 3.29) and SGA (OR, 1.54; 95% CI, 1.08 to 2.19), and there was also a significant test for trend ($P < 0.001$). However, there was no significant association with BW or gestational age. When using other estimates for kidney function, no significant association was found.

Table 4 lists the effect of IUGR on kidney function as a continuous variable by using linear regression analysis. In men, there was a significant association between BW and all kidney function estimates. When BW increased by 1 kg, creatinine clearance increased by 7.3 mL/min (0.12 mL/s; 95% CI, 6.0 to 8.6). However, there was no association with gestational age, and the association with BW adjusted for gestational age was weaker than with crude BW. Creatinine clearance increased by 4.0 mL/min (0.07 mL/s; 95% CI, 3.3 to 4.6) per 1-SDS increase in BW. Adjustment for potential confounders, such as maternal risk factors (age, diabetes, kidney disease, and a preeclamptic pregnancy), adult smoking, and educational level did not change the strength of the observed associations. In women, there was also a significant, but less strong, association between BW and kidney function. When BW increased by 1 kg, creatinine clearance increased by 5.5 mL/min (0.09 mL/s; 95% CI, 4.2 to 6.8). There was no association with gestational age, and the association with BW adjusted for gestational age was weaker: creatinine clearance increased by 2.9 mL/min (0.05 mL/s; 95% CI, 2.2 to 3.5) per 1-SDS increase in BW. There was no significant association when estimating kidney function using the MDRD Study equation (in milliliters per minute per 1.73 m²). Results of multiaadjusted analyses were very similar to those of age-adjusted analyses.

Table 5 lists the effect of BW on blood pressure. Systolic blood pressure decreased by 0.74

Table 5. Association between birth weight and blood pressure at a young adult age observed in HUNT 2 participants born 1967-1976

	Change in Blood Pressure			
	Men		Women	
	/1 kg BW	/1 BW-SDS	/1 kg BW	/1 BW-SDS
Systolic blood pressure (mm Hg)				
Adjusted for age	-0.74 (-1.45 to -0.02)	-0.38 (-0.75 to -0.01)	-1.27 (-1.96 to -0.59)	-0.57 (-0.91 to -0.24)
Adjusted for age and potential confounders	-0.51 (-1.26 to 0.25)	-0.24 (-0.63 to 0.15)	-1.50 (-2.22 to -0.79)	-0.69 (-1.05 to -0.34)
Adjusted for age, potential confounders, and adult weight	-1.52 (-2.26 to -0.77)	-0.81 (-1.19 to -0.43)	-2.35 (-3.05 to -1.65)	-1.15 (-1.50 to -0.81)
Diastolic blood pressure (mm Hg)				
Adjusted for age	-0.16 (-0.68 to 0.36)	-0.16 (-0.43 to 0.10)	-0.68 (-1.18 to -0.17)	-0.42 (-0.66 to -0.17)
Adjusted for age and potential confounders	0.05 (-0.50 to 0.60)	-0.05 (-0.33 to 0.23)	-0.69 (-1.21 to -0.16)	-0.41 (-0.67 to -0.15)
Adjusted for age, potential confounders, and adult weight	-0.49 (-1.04 to 0.06)	-0.35 (-0.64 to -0.07)	-1.10 (-1.62 to -0.57)	-0.64 (-0.90 to -0.38)

Note: The association (95% confidence interval) between BW-SDS and blood pressure was assessed in an age-adjusted linear regression analysis. Maternal risk factors (age, diabetes, kidney disease, and preeclampsia) and current smoking and education were considered as potential confounders and adjusted for. We also adjusted for adult weight to illustrate the effect of considering this variable as a confounder.

Abbreviations: HUNT 2, Nord Trøndelag Health; BW, birth weight; SDS, SD score.

mm Hg (95% CI, 0.02 to 1.45) for each 1-kg increase in BW in men and by 1.27 mm Hg (95% CI, 0.59 to 1.96) in women after adjustment for age at the HUNT 2 examination. The decrease was 0.38 mm Hg (95% CI, 0.01 to 0.75) for each 1-SDS increment in BW adjusted for gestational age in men and 0.57 mm Hg (95% CI, 0.24 to 0.91) in women. Diastolic blood pressure did not decrease significantly in men, but in women, it decreased 0.68 mm Hg (95% CI, 0.17 to 1.18) for each 1-kg increase and 0.42 mm Hg (95% CI, 0.17 to 0.66) for each 1-SDS increment in BW. Exclusion of subjects administered antihypertensive medication did not change results. Adjustment for maternal risk factors (age, diabetes, kidney disease, and preeclampsia), current smoking, and education at adult age resulted in only minor changes in the observed associations, whereas adjustment for adult weight increased the coefficients significantly.

Discussion

In this population-based study, we found that subjects born after IUGR had an increased risk of low-normal kidney function at a young adult age. When adjusting BW for gestational age, creatinine clearance decreased by 4.0 mL/min (0.07 mL/s) in men and 2.9 mL/min (0.05 mL/s) in women per 1-SDS decrease. If intrauterine growth was expressed as crude BW, creatinine clearance decreased by 7.3 mL/min (0.12 mL/s) in men and 5.4 mL/min (0.09 mL/s) in women per 1-kg decrease in BW.

Several method issues need discussion. Kidney function was not measured directly, and although the methods used for estimating kidney function previously were found to be unbiased in the present study group,²⁶ their accuracy is only moderate and misclassification can occur. Urine albumin is another important marker of kidney damage, but this was available for only a subgroup of participants and could not be used in our analyses. An optimal diagnosis of IUGR requires repetitive measurements of fetal growth parameters by using ultrasound. However, in epidemiological studies of larger numbers of pregnancies, such as ours, this procedure was not feasible; therefore, the concept of SGA was used as a proxy of IUGR. Because this reflects only the situation at birth, there will be some misclassification because not all SGAs result from IUGR and some non-SGAs experienced IUGR.

It is well documented that subjects with IUGR have lower adult height, lower muscle mass, and higher fat content.^{28,29} Because of this body composition, they might have serum creatinine values that are underestimated and weights that are overestimated relative to height. Because the Cockcroft-Gault formula is based on the product of these 2 variables, it is conceivable that they balance each other and therefore give a reliable estimate of kidney function. However, overestimation or underestimation is also possible. The MDRD Study equation

might overestimate kidney function in subjects with IUGR, and a possible low-normal kidney function will be veiled, rendering the observed ORs conservative. Formulas including lean body mass could have been well suited for this research question,³⁰ but information for lean body mass was not available.

Furthermore, instead of expressing kidney function traditionally per surface area, some recommend to adjust for body size in the regression analysis.³¹⁻³³ This is controversial in “fetalorigin” studies because such body size variables as extracellular volume, body surface area, and body mass index are influenced by central obesity, which must be considered as an intermediate variable in the causal pathway between IUGR and later kidney function. Adjustment for height is suggested because smaller body size might require less absolute kidney filtration, but the use of noncorrected kidney function estimates is recommended until these problems are clarified further.²³ We therefore used Cockcroft-Gault estimates (milliliters per minute) as our primary outcome, but also used other estimates of kidney function. Especially in men, all outcome variables were consistently associated with BWSDS, indicating that the relation between BW and kidney function probably is not caused by chance finding or bias. However, in women, associations were less strong. Nonresponse may lead to selection bias. However, participants and nonparticipants did not differ in perinatal characteristics, thereby making an effect of selection bias less likely. Estimating gestational age based on date of last menstrual period is prone to error, but sonographic estimates were not routinely performed in Norway in the 1970s. A major strength of our study is the prospective design. Furthermore, the completeness of the perinatal registration enabled us to adjust BW for gestational age, which is considered important to obtain a valid measure of a subjects’s exposure to IUGR.^{7,34-36}

We found that IUGR was associated with low-normal kidney function in young adults from the general population. This is consistent with findings in subjects born very prematurely¹⁷. A low nephron number was observed in low-BW subjects at autopsy. This could explain associations of low BW with such clinical outcomes as albuminuria, low-normal kidney function, and ESRD.^{6-17,37} However, these are only a few studies, sometimes with a weak design, and the effects found were not strong. Case-control studies showed an OR of 1.5 for ESRD in subjects with BWs less than 2,500 g, but data for BW were missing in half the cases.^{15,37}

Blood pressure was used as a secondary outcome because of the central role of the kidneys in blood pressure regulation, and IUGR is also postulated to lead to hypertension and reduced kidney function through a decreased number of nephrons.⁵ We found that systolic blood pressure increased by 0.7 to 1.3 mm Hg per 1-kg decrease in BW. This is in accordance with 2 large meta-analyses that found systolic blood pressure increased by 1 to 2 mm Hg per 1-kg decrease in BW^{38,39} and strengthens the external validity of our results. Earlier studies reported much larger associations, eg, an increase in systolic blood pressure of 11

mm Hg per 1-kg lower BW in middle-aged subjects.¹ These early more radical conclusions most likely reflect random error, publication bias, and inappropriate adjustment for current weight.³⁸ Theoretically, if there was no correlation between BW and adult blood pressure, but both positively correlated with adult body size, adjusting for adult body size could induce a negative correlation between BW and blood pressure.⁴⁰ Our study shows that such adjustment clearly increased the magnitude of the association, but did not create it. Others also found similar results,³⁹ and noting that low BW is associated with low adult weight, which in turn is associated with lower blood pressure, it is not yet clear how to solve this problem.

Sex was reported to modulate the effect of IUGR in many experimental animal models.⁴¹⁻⁴³ In different species and using different methods for creating an adverse fetal environment, male offspring consistently experienced worse outcomes. Our findings are in accordance with these results. The analysis of discrete outcomes showed nearly no association between IUGR and low normal kidney function in women, but analysis of continuous outcomes showed a general effect, although weaker, in women as well, which can be related to the greater power present with continuous data. Consequently, the intrauterine origin of adult disease hypothesis may be of greater importance in men than women. Still, bias caused by kidney function estimation methods veiling an effect also in females cannot be ruled out; the effect of IUGR on blood pressure was present in both men and women.

The impact of low BW on public health in developed countries has been questioned.⁴⁴ The question remains whether IUGR causes adult disease or IUGR is caused by a factor that also causes adult disease, either of genetic or permanent environmental nature. In the latter case, IUGR predicts rather than causes adult disease. Irrespective of mechanisms, our findings, even if effects are small, may have important implications. Small effects found at a young adult age may progress to larger effects at older ages because the kidney and vasculature no longer may be able to compensate with hyperfiltration, vasodilatation, and antioxidant pathways. Such amplification throughout life was clearly shown for blood pressure.^{39,45}

Moreover, the potential effect of intervention can be different in developing countries. Mean BW is nearly 1 kg less in South Asia compared with western Europe.⁴⁶ Modifiable factors, such as shortage of food, micronutrient deficiencies, sex discrimination, and intentionally decreased food intake during pregnancy because of cultural beliefs may be of greater importance for BW than racial differences *per se*.^{35,47,48} Although most fetal origins of adult disease studies were conducted in white populations, an increasing number of studies from China and India confirm the influence of low BW on adult blood pressure, glucose metabolism, and other cardiovascular risk factors.⁴⁹⁻⁵² Mortality and morbidity from coronary artery disease, diabetes mellitus, and chronic kidney disease are expected to increase by 200% to 400% in developing countries during the next 30 years because of increased longevity and adverse

lifestyle changes.^{53,54} These estimates, which are based on changes in demographic and lifestyle factors alone, could even be too conservative because a large proportion of these populations were exposed to IUGR.

In conclusion, we found that IUGR was associated with low-normal kidney function in this large Norwegian population-based cohort study. The association was stronger in men than women and persisted after adjusting for potential important perinatal confounders. Although the absolute effects found were small, our results may have important etiologic implications.

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