Microalbuminuria and Lower Glomerular Filtration Rate at Young Adult Age in Subjects Born Very Premature and after Intrauterine Growth Retardation

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This prospective follow-up study of 422 19-yr-old subjects born very preterm in The Netherlands was performed to determine whether intrauterine growth retardation (IUGR) predisposes to abnormal GFR and microalbuminuria in adolescents. GFR (ml/min per 1.73 m^2) was estimated using the Cockcroft-Gault equation, and albumin-creatinine ratio (mg/mmol) was calculated in a cohort of 19-yr-old subjects born very preterm (gestational age <32 wk) in 1983. Birth weights were adjusted for gestational age and expressed as standard deviation scores (sds) as a measure of IUGR. All subjects had normal renal function. Birth weight (sds) was associated negatively with serum creatinine concentration (μmol/L) ($\beta = -1.0$ μmol/L, 95% confidence interval [CI]: −1.9 to −0.2), positively with GFR ($\beta = 3.0$, 95% CI: 1.7 to 4.2), and negatively with the logarithm of albumin-creatinine ratio ($\beta = -0.05$, 95% CI: −0.09 to −0.01) in young adults born very preterm. IUGR is associated with unfavorable renal functions at young adult age in subjects born very premature. These data suggest that intrauterine growth–retarded subjects born very premature have an increased risk to develop progressive renal failure in later life.

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Fetal kidney development is known to be impaired in subjects liable to intrauterine growth retardation (IUGR). In both animal and human studies it was shown that neonatal kidney volume and nephron number is reduced when intrauterine growth was impaired (1–5). Offspring of Sprague-Dawley rats, which were kept on a low-protein diet during pregnancy, had a 28 to 29% decreased number of glomeruli in proportionally smaller kidneys (6). Also, BP was increased 8 wk after birth. Mañalich *et al.* described less glomeruli in the renal cortex per 0.6 mm^2 in low birth weight (BW) neonates who died within 2 wk after birth due to diseases not involving the kidneys (7). In this study there was a direct relation found between BW and number of glomeruli.

It has been suggested that low BW and impaired nephron number at birth increases the risk of renal failure and ESRD in later life (8,9). Brenner *et al.* suggested that the filtration surface area in kidneys with low nephron number is decreased compared with healthy subjects with normal nephron number. This decrease in filtration surface area would lead to glomerular and systemic hypertension, glomerular damage, and sclerosis, and therefore to a decrease in renal function (hyperfiltration theory) (10). One of the first symptoms of developing renal disease is microalbuminuria preceding decrease in GFR.

Recently, data have been published showing a strong relation between BW and renal size, nephron number, glomerular volume, albuminuria, and systolic BP in aboriginal communities (11,12). In communities of aboriginals and Indians, diseases like type II diabetes, cardiovascular diseases, and renal diseases take epidemic proportions (13,14). Poverty and poor living conditions leading to low BW in the offspring are suggested to be important in the development of these diseases (15).

It has been shown that preterm-born subjects have smaller kidneys than subjects born at term. As nephrogenesis continues until 36 wk of gestation, subjects born very prematurely are suggested to have less glomeruli at birth than subjects born less preterm. Recently, it was also shown that nephrogenesis ceases after very preterm birth (16).

The combination of prematurity and IUGR, which often are both present, might even further increase the risk for progressive renal failure. Data on renal function at adult age in subjects born very preterm is very scarce.

We describe the results of a large-scale prospective follow-up study in subjects born with a gestational age <32 wk in 1983 in The Netherlands, in which we estimated GFR and measured

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See Appendix for a list of Dutch POPS-19 Collaborative Study Group participants.

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microalbuminuria at the age of 19 yr. The objective was to evaluate the effect of IUGR in these preterm subjects on renal function at young adult age. In addition, we evaluated the effect of gestational age, in the lowest ranges of gestation, on renal function at young adult age.

Materials and Methods

Study Population

In a prospective follow-up study carried out from April 2002 until May 2003, all survivors of the POPS cohort (Project on Prematures and Small for Gestational Age Infants) born with a gestational age <32 wk were invited to visit one of ten outpatient clinics in The Netherlands, at the age of 19 yr. The POPS cohort was recruited in 1983, where 94% of all Dutch neonates, born alive with a gestational age (GA) <32 wk and/or a BW <1500 g were included (n = 1338) (17). All subjects alive at the age of 19 yr (n = 959) and not lost to follow up (n = 25) were invited to participate in a prospective follow-up study. For this part of the study only subjects born with a gestational age <32 wk (n = 676) were eligible to participate.

Data Obtainment

Two morning urine samples were collected to measure creatinine and microalbumin concentrations to calculate albumin-creatinine ratio (ACR). Female subjects within their menstrual period at time of urine collection were excluded from the analyses of ACR. A blood sample was obtained to measure creatinine, urea, sodium, and potassium concentrations.

GFR was calculated both with the Cockcroft-Gault equation, adjusted for body surface area (ml/min per 1.73 m^2), and with the simplified MDRD equation (18,19). ACR (mg/mmol) was calculated in morning urines as a measure of microalbuminuria (<2.2, normal; 2.2 to 22.6, microalbuminuria; >22.6, macroalbuminuria or proteinuria) (20). The average ACR in two morning urines was calculated and used in the analyses. When only one morning urine was obtained, that result was used.

Sodium, potassium, creatinine, and urea were measured in a fully automated computerized laboratory system with a Hitachi 747 chemistry analyzer (Hitachi, Tokyo, Japan). Microalbumin was measured with a turbidimetric assay on a Hitachi 911 (Hitachi).

Perinatal parameters (*i.e.*, BW, GA, Apgar score) and obstetric parameters (*i.e.*, maternal hypertension, use of medication during pregnancy, smoking during pregnancy) were derived from the original POPS database (TNO Quality of Life, Leiden, The Netherlands). These parameters were obtained in 1983 directly after birth. GA (best obstetric estimate) was based on last menstrual period, pregnancy testing, and ultrasound (if necessary). This was available in 1335 cases. The reliability of this estimate was stated to be excellent in 78% of cases; in only 7% there was a discrepancy of 2 wk or more with the pediatric assessment (pediatric maturity score = Dubowitz score), which is well within the variability of the scoring systems (17).

BW adjusted for GA and adult weight were converted to standard deviation scores (sds), using Swedish and Dutch reference standards (21,22). Subjects with a BW-sds <0 were defined as small for gestational age (SGA) and subjects born with a BW-sds ≥0 were defined as appropriate for gestational age (AGA). BW-sds was considered as a measure of IUGR.

Informed Consent and Ethics Committee

Informed consent was obtained after oral and written information had been given. The ethics committees of all participating centers approved the study protocol.

Statistical Analyses

Standard methods were used for calculation of the mean, SD, SEM, and the 95% confidence intervals (CI). To study the effect of BW-sds on renal function, independent of adult weight (sds), we used a multivariate regression model. In fact, we were interested in the effect of growing more than would be expected from a given BW. Therefore, we first calculated the expected adult weight (sds) based on BW-sds, and then subtracted the actual adult weight (sds). This residual was entered in the regression model (23), leading to an effect of adult weight (sds) independent of BW-sds. The algebraic concept of this regression model is recently explained (24). The coefficient of BW-sds shows the effect of BW-sds on the outcome, and the coefficient of the residual adult weight shows the effect of gaining more weight than expected on the outcome. In all regression models we adjusted for gender. Statistical significance was defined when the P value was <0.05.

Results

Of 676 eligible subjects, 422 participated (46.7% males) in this study (response rate, 62.4%). Subject characteristics are shown in Table 1. The mean (SD) age was 19.3 (0.2) yr. The mean (SD) BW was 1317 (338) g, gestational age was 29.7 (1.5) wk, and the BW-sds was −0.11 (1.02). Sodium, potassium, and urea concentrations were in normal range in all subjects and equal in the SGA and AGA group.

Regression coefficients (adjusted for gender) of BW (both sds and grams) and GA on renal function parameters are summarized in Tables 2 and 3. The effect of adult weight (sds) independent of BW-sds is also shown in Table 2.

Creatinine Concentration and GFR

The mean (SD) serum creatinine concentration (n = 396) was 81 μmol/L (10). All values were within normal range (51 to 115 μmol/L). Serum creatinine concentration was inversely related to BW-sds (β = −1.0; 95% CI: −1.9 to −0.2); so serum creatinine concentration was highest in subjects with lowest BW (for GA). This relation was equal in males and females. However, creatinine concentration was 10.64 μmol/L higher in males compared with females (95% CI for mean difference: 8.9 to 12.4, P < 0.001). Figure 1 shows the relation between BW-sds and serum creatinine concentration in males (Figure 1A) and females (Figure 1B).

Cockcroft-Gault GFR (CG GFR) was available for 388 subjects. The mean (SD) GFR was 107.0 (15.8) ml/min per 1.73 m^2 ranging between 76.7 and 210.7 ml/min per 1.73 m^2. The mean GFR was 6.4 ml/min per 1.73 m^2 higher in males than in females (95% CI: 3.3 to 9.5). When the MDRD equation was used, the mean GFR (SD) was 98.0 (14.7) ml/min per 1.73 m^2, ranging between 64.2 and 162.5 ml/min per 1.73 m^2. Also, the MDRD GFR was 14.3 ml/min per 1.73 m^2 higher in males than females.

Both CG GFR and MDRD GFR were positively related to BW-sds (Figure 2), meaning that subjects with low BW (for GA) have lower GFR values than subjects with high BW (for GA). The coefficient for the CG equation was 3.0 ml/min per 1.73 m^2 (95% CI: 1.7 to 4.2) and for the MDRD equation 1.2 ml/min per 1.73 m^2; 95% CI: 0.0 to 2.5). Also, adult weight (sds) was, independent of BW, highly associated to CG GFR (β = 6.2; 95%

Table 1. Patient characteristics[a]

	All Subjects $n = 422$	SGA (BW-sds < 0) $n = 215$	AGA (BW-sds ≥ 0) $n = 207$	P Value (t test)
Age, yr	19.3 (0.2)	19.3 (0.2)	19.3 (0.2)	0.323
Males, number (%)	197 (46.7%)	91 (42.3%)	106 (51.2%)	0.068 (χ^2)
BW, g	1317 (338)	1144 (259)	1496 (317)	<0.001
GA, wk	29.7 (1.5)	30.0 (1.4)	29.4 (1.6)	<0.001
BW-sds	−0.11 (1.0)	−0.87 (0.78)	0.68 (0.49)	<0.001
BMI*	21.74 (3.4)	22.01 (3.4)	21.94 (3.3)	0.113
Serum creatinine, μmol/L[b]	81.8 (10.2)	81.9 (9.8)	81.7 (10.6)	0.862
CG GFR, ml/min per 1.73 m^2[b]	107.0 (15.8)	105.1 (16.0)	108.9 (15.4)	0.018
MDRD GFR, ml/min per 1.73 m^2[b]	98.0 (14.7)	96.6 (13.6)	99.4 (15.8)	0.064
Serum urea, mmol/L[b]	4.6 (1.1)	4.6 (1.1)	4.6 (1.2)	0.739
Serum sodium, mmol/L[b]	143 (3)	143 (3)	143 (3)	0.681
Serum potassium, mmol/L[b]	4.5 (0.4)	4.5 (0.4)	4.5 (0.5)	0.919
log ACR, log(mg/mmol)[b]	−0.69 (0.40)	−0.74 (0.36)	−0.64 (0.44)	0.015
Geometric ACR, mg/mmol	0.20 (2.52)	0.18 (2.27)	0.23 (2.77)	

SGA, small for gestational age; AGA, appropriate for gestational age; BW, birth weight; GA, gestational age; BW-sds, birth weight adjusted for gestational age expressed by standard deviation scores; CG GFR, Cockroft-Gault GFR; MDRD GFR, simplified MDRD GFR; ACR, albumin-creatinine ratio (log ACR values and the geometric values of these log transformations are shown).

[a]Data expressed by mean ± standard deviation, except when noted differently. P-values based on t test, comparing AGA and SGA subjects. In the distribution of males and females χ^2 test was used.

[b]Number of subjects ranges between 368 and 414.

Table 2. Regression coefficients of BW-sds with 95% CI and P values adjusted for residual adult weight and gender

	Coefficient of BW-sds	95% CI	P Value	Coefficient of Residual Adult Weight (sds)	95% CI	P Value	Mean Increase in Males	95% CI	P Value
Serum creatinine, μmol/L	−1.046	−1.886 to −0.206	0.015	0.146	−0.510 to 0.801	0.663	11.067	9.380 to 12.753	<0.001
CG GFR, ml/min per 1.73 m^2	2.954	1.665 to 4.243	<0.001	6.240	5.236 to 7.245	<0.001	6.24	5.236 to 7.245	<0.001
MDRD GFR, ml/min per 1.73 m^2	1.230	0.003 to 2.458	0.050	−0.127	−1.085 to 0.831	0.794	13.587	11.122 to 16.052	<0.001
log ACR[a]	−0.051	−0.092 to −0.010	0.016	−0.005	−0.037 to 0.027	0.758	−0.002	−0.085 to 0.080	0.958

[a]Interpretation of the equation for ACR: ACR (mg/mmol) = $10^{(-0.051 \times \text{BW-sds})}/10^{(-0.005 \times \text{residual adult weight})}/10^{-0.002}$ if male. Without adjustment for residual weight and gender, the coefficient and 95% confidence interval (CI) for BW-sds to log ACR is nearly equal (−0.050, 95% CI: −0.091 to −0.010).

CI: 5.2 to 7.2) but not to MDRD GFR ($\beta = -0.1$; 95% CI: −1.1 to 0.8).

BW was also related to serum creatinine concentration and GFR. An increase of 100 g in BW corresponded with a decrease of serum creatinine concentration of 0.39 μmol/L (95%CI: −0.642 to −0.127) and an increase in GFR of 1.129 ml/min per 1.73 m^2 (95% CI: 0.672 to 1.586).

Creatinine concentration and GFR were not related to GA ($\beta = -0.2$; 95% CI: −0.7 to 0.4 for creatinine concentration and $\beta = 0.9$; 95% CI: −0.2 to 1.9 for GFR). Data are shown in Table 3.

Microalbuminuria

One or two morning urines were available in 404 subjects. Thirty-one female samples were excluded from data analyses because the urine was obtained during their menstruation period. In five subjects data on laboratory results were missing, leaving 368 subjects for data analyses. In 77 subjects only one morning urine was available for analyses. The mean ACR did not differ from the average ACR in subjects with two available morning urines (mean difference 0.14 mg/mmol, 95% CI: −0.29 to 0.56).

Table 3. Regression coefficients of birth weight and gestational age on outcome with 95% CI and *P* values adjusted for gender

	BW (per 100 g)	95% CI	*P* Value	GA (wk)	95% CI	*P* Value
Serum creatinine,	−0.385	−0.642 to −0.127	0.004	−0.171	−0.741 to 0.399	0.556
μmol/L	in males: +11.083	9.359 to 12.806	<0.001	in males: +10.636	8.921 to 12.352	<0.001
CG GFR,	1.129	0.672 to 1.586	<0.001	0.854	−0.167 to 1.875	0.101
ml/min per 1.73 m^2	in males: +5.153	2.102 to 8.204	0.001	in males: +6.428	3.341 to 9.515	<0.001
MDRD GFR,	0.412	0.027 to 0.797	0.036	0.023	−0.826 to 0.872	0.957
ml/min per 1.73 m^2	in males: +14.314	13.839 to 11.263	<0.001	in males: +14.314	11.762 to 16.866	<0.001
log ACR	−0.019	−0.031 to −0.006	0.003	−0.015	−0.042 to 0.012	0.288
	in males: +0.016	−0.073 to 0.094	0.802	in males: +0.012	−0.095 to 0.070	0.773

BW, coefficient of actual birth weight (per 100 g) on outcome; GA, coefficient of gestational age (per week) on outcome. Interpretation of the equation for ACR and BW: ACR (mg/mmol) = $10^{(-0.019 \times \text{BW per 100 g})} \times 10^{0.016}$ if male.

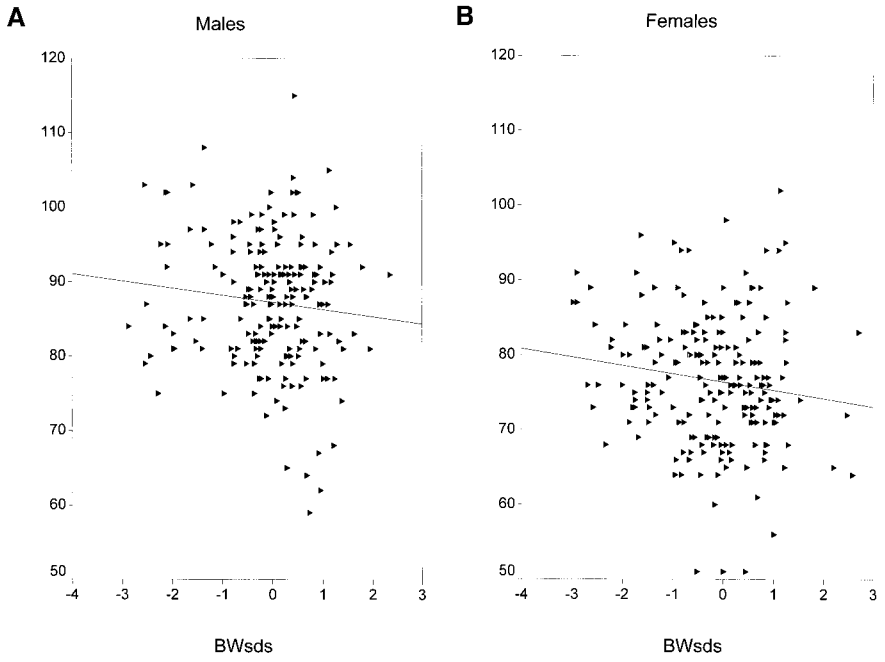

*Figure 1.*Scatterplot between birth weight standard deviation scores (BW-sds) and serum creatinine concentration in males (A) and females (B) at the age of 19 yr. sds, standard deviation scores.

The prevalence of microalbuminuria (ACR > 2.2 mg/mmol) in the total group was 2.7% (Table 4). The prevalence in SGA subjects (3.8%) was 2.4 times higher (95% CI: 0.6 to 9.3) than in the AGA subjects (1.6%). The mean (SD) ACR in SGA subjects was 0.51 (1.43) mg/mmol and in the AGA subjects 0.29 (0.54) mg/mmol (mean difference; 0.21 mg/mmol [95% CI: −0.01 to 0.44]). This trend was confirmed in a regression model, showing that subjects with lower BW-sds had higher ACR values compared with subjects with higher BW-sds (β = −0.11; 95% CI: −0.22 to 0.01). As the distribution of ACR was left-side skewed (mean [SD]: 0.40 [1.09]; range: 0.04 to 15.14; skewness: 9.3), we examined whether the relation remained present after logarithmic transformation (log-ACR mean [SD]: −0.7 [0.4], range: −1.44 to 1.18; skewness: 1.3). BW-sds was still significantly related to ACR (ACR = $10^{-0.05 \times \text{BW-sds}}$; 95% CI for β: −0.09 to −0.01) as shown in Figure 3 (P = 0.02). ACR also decreased with increase of actual BW (per 100 g) (ACR = $10^{-0.02 \times \text{BW per 100 g}}$; 95% CI for β: −0.03 to −0.01). GA was not related to microalbuminuria in our study (Table 3).

Discussion

We have found an association between the extent of IUGR and renal functions of young adults born very prematurely (GA < 32 wk). On average, our subjects born with low BW-sds had lower GFR, higher serum creatinine concentration and higher microalbumin excretion at the age of 19 yr. These associations were independent of adult weight (sds).

Controversy exists regarding which equations for GFR estimates real GFR best. The CG equation is suggested to be more accurate in healthy subjects with normal GFR values, but is

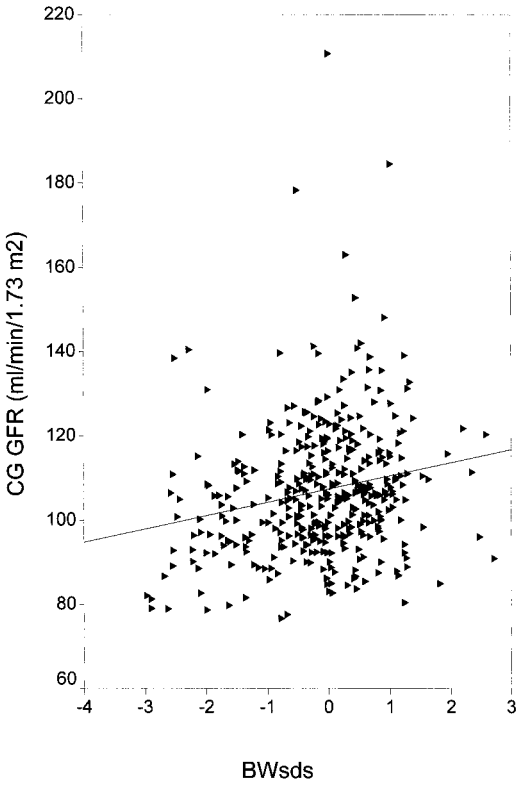

Figure 2. Scatterplot between BW-sds and Cockroft-Gault GFR (CG GFR) at the age of 19 yr.

dependent on adult weight (25). The (simplified) MDRD formula is not dependent on adult weight, but is based on patients with renal dysfunction and therefore is suggested as less reliable in healthy individuals. To estimate GFR, the CG equation is most commonly used in clinical settings in adults. Adult weight was a very strong predictor for CG GFR, acting as a factor in the causal pathway when multivariate regression analysis is used. Using the multivariate regression analysis with residuals, as explained in Statistical Analyses, the influence of this causal pathway factor was prevented. The relation between BW-sds and GFR we found was therefore not influenced by adult weight (sds). Moreover, both CG and MDRD GFR estimations show a positive significant relation between BW-sds and GFR, with a 1.2 to 3.0 ml/min per 1.73 m^2 increase in GFR per 1 BW-sds increase.

In this study, actual BW (grams) was related to renal outcome at 19 yr. However, no convincing relation between GA (up to 32 wk of age) and renal function was found. Therefore, it is most likely that BW (grams) is not actually the important predicting factor for renal outcome, but indeed the extent of IUGR (BW-sds). If not, the relation between GA and renal function would have been much stronger.

A potential selection bias may have been introduced as a result of a response of 62.4%. Nonresponders were hard to trace or not willing to participate, mainly due to a lack of time, lack of interest, or fear of medical examination. Unfortunately, specific information on renal function, renal diseases, and renal deaths in nonresponders were not available. However, BW, GA, and BW-sds were not significantly different between responders and nonresponders. Therefore the effect of a potential selection bias on our results is probably limited.

Our findings suggest the possibility that the normal process of aging, with a decline of GFR after the age of 20 yr (26), may be enhanced after IUGR and preterm birth. We cannot predict if and how much the relation between BW-sds and renal function will strengthen with age. To study the effect on the incidence of renal function decline and renal disease in later life, follow-up of our cohort is recommended.

Our results are in agreement with several animal studies, showing that renal function is decreased after IUGR (4,27). Also, several human studies have linked IUGR with renal function (8,9,12). In the Saskatchewan population in Canada, women with ESRD were three times more likely to have had low BW compared with subjects without ESRD (8). In this study, increase in maternal age, known as a risk factor for prematurity and low BW, was also related to ESRD of the offspring at adult age. Lackland *et al.* described a U-shaped quadratic association between BW and early-onset of chronic renal failure in subjects living in the southeast of the United States (9). In this study, differences in gender or race were not seen. However, as low BW is suggested to be more common in black people and in the southeastern part of the United States, this may explain the increased prevalence of ESRD in that region. Another recent study of 668 aboriginal subjects between 4 and 72 yr of age showed that subjects with the lowest BW had smallest kidneys (measured by ultrasound), and the subjects with the smallest kidney size had the highest BP and the highest rates of albuminuria (ACR $\geq$ 34 mg/mmol) (11). Also, nephron number was inversely related to glomerular volume, suggesting that glomerulomegaly is a marker of an increased risk of groups of patients or populations with progressive renal disease (3). These studies all show that in these populations at risk for ESRD, BW is lower, supporting the hyperfiltration theory as a possible mechanism, in that IUGR is a risk factor for the development of progressive renal disease (10).

In our study the overall prevalence of microalbuminuria was 2.7%. This prevalence was two times higher in SGA subjects than in AGA subjects. In a linear regression analysis we confirmed a relation between BW and microalbuminuria. SGA subjects have an increased risk for higher microalbumin concentrations, and therefore may be at risk to develop real microalbuminuria later in life.

The relationships between BW-sds and renal function in our study are weak, and do not have clinical implications for the subjects at this age. The knowledge of decrease in GFR after the age of 20 yr and the increase in the prevalence of microalbuminuria, and therefore the risk for developing progressive renal disease, shows the importance of these small differences at this young age (26,28). Follow-up of our cohort is recommended to trace subjects with early decrease in renal function and to study whether the relation between BW-sds and renal function will straighten with increase of age.

In conclusion, our data support the hypothesis that in subjects born prematurely, IUGR affects renal development in an

Table 4. Distribution of microalbuminuria in morning urines

	All subjects		SGA (BW-sds < 0)		AGA (BW-sds ≥ 0)	
	Number	%	Number	%	Number	%
No microalbuminuria (ACR < 2.2)	358	97.3%	178	96.2%	180	98.4%
Microalbuminuria (ACR > 2.2 and ACR < 22.6)	10	2.7%	7	3.8%	3	1.6%
Total	368	100%	185	100%	183	100%

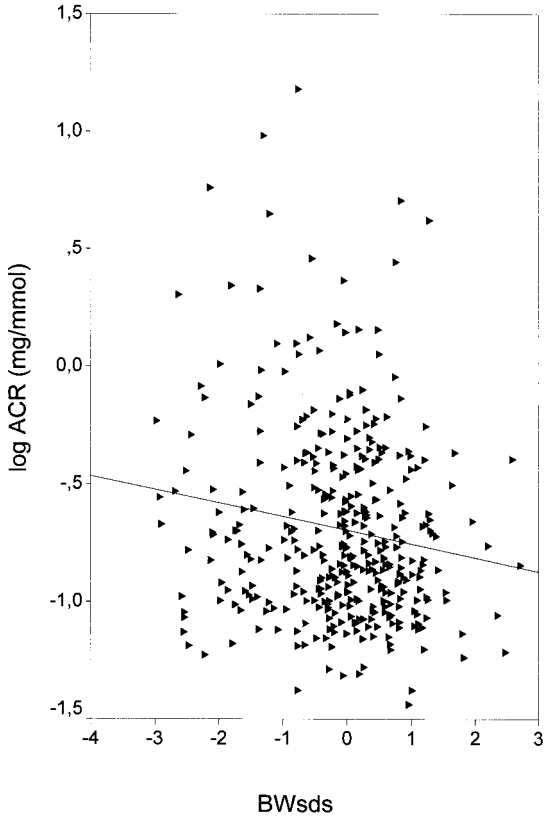

Figure 3. Scatterplot between BW-sds and the logarithm of albumin-creatinine ratio (ACR) at the age of 19 yr.

unfavorable way, possibly leading to progressive renal failure in later life.

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Appendix

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