

RESEARCH ARTICLE

Renal function and blood pressure in 11 year old children born extremely preterm or small for gestational age

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Data Availability Statement: Data from the study are available upon request, as there are legal restrictions on sharing these data publicly due to the data containing sensitive and identifiable information. The data set contains information like birthweight, gestational age, birth data and gender - information that may be used to directly identify individuals, as Norway is a small country and our health region even smaller, and as extremely preterm birth applies to relatively few individuals in each hospital each year. In the informed consents signed by the guardians of the participant of this

Abstract

Background

Preterm birth and low birth weight are associated with reduced nephron numbers and increased risk of hypertension and kidney disease in later life.

Aims

We tested the hypothesis that extremely preterm birth and intrauterine growth restriction is associated with decreased renal function in mid childhood.

Methods

At 11 years of age the following measures were obtained in a regional cohort of children born extremely premature (EP, i.e. < 28 weeks gestational age—GA) or with extremely low birth weight (ELBW, i.e. BW < 1000 grams) and in matched controls born at term with appropriate BW (AGA): Height, weight, abdominal circumference, triceps and subscapular skin fold thicknesses, blood pressure, plasma levels of creatinine, cystatin C and symmetric dimethyl arginine (SDMA). Small for gestational age (SGA) was defined as a BW < 10th percentile for GA. Glomerular filtration rate (GFR) was estimated according to the equations by Schwartz, Zappitelli and Gao.

Results

Fifty-seven of 61 eligible EP/ELBW children, 20 (35%) born SGA, and 54 controls, were assessed. Estimated GFR decreased while plasma SDMA increased from the children born AGA at term through those born preterm AGA to preterm SGA. Systolic BP was correlated to fat mass indices (p<0.03), but not to renal function (p>0.2) and did not differ between the groups.

study, and granted by the regional committee for medical ethics in Helse Vest, guardians were not asked about data sharing. Researchers interested in the data may contact the person safety representative in Helse Bergen (Christer.kleppe@helse-bergen.no) and the ethics committee that approved the study (post@helseforskning.etikk.no).

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Competing interests: Bevtal A/S provided financial support in the form of salaries for KM and ØM, and research materials. This does not alter our adherence to the PLOS ONE policies on sharing data and materials.

Abbreviations: AGA, Appropriate weight for Gestational Age; BW, Birth Weight; EP, extremely preterm; ELBW, extremely low birth weight; G, Grams; GA, Gestational Age; IQR, Interquartile Range; LBW, low birth weight; SD, Standard Deviation; SGA, Small for Gestational Age; CRP, C-Reactive Protein; GFR, Glomerular Filtration Rate; BP, Blood Pressure; BMI, Body Mass Index.

Conclusions

Children born EP/ELBW, particularly those born SGA, had impaired renal function at age 11 years as judged from estimated GFRs and plasma levels of SDMA. Since reduced renal function is associated with an increased risk of later disease, these children should be followed in order to minimize additional risk factors.

Introduction

Preterm birth implies short- and long-term consequences for most organ systems. The fetus might have been subject to adverse intrauterine development leading to preterm birth [1], and thereafter has to finalize growth and development outside the uterus, often in a neonatal intensive care unit, exposed to a range of internal and external stressors with the potential to induce harm [2]. Remarkable improvements in survival for preterm born children the last few decades have resulted in large cohorts of long-term survivors. Their health is of increasing public relevance [3, 4], as late morbidity might be increasing in these populations as they grow older. This calls for research into long-term risks in preterm populations.

For the renal system, being born preterm, with low birth weight (LBW, i.e. < 2500 gram) or small for gestational age (SGA, i.e. BW < 10th percentile for GA), is associated with smaller kidneys, reduced nephron numbers, possibly morphologically abnormal nephrons and reduced glomerular filtration rate [5]. This implies an increased risk of developing hypertension (HTN) and chronic kidney disease (CKD) in later life [5–9]. Thus, early diagnosis of renal dysfunction is warranted in order to minimise additional risk factors for CKD [10].

The gold standard for assessment of renal function is *glomerular filtration rate (GFR)* based on the clearance of the exogenous marker inulin, but also clearance of iothalamate and iohexol are used [11]. While these methods are expensive, time consuming and associated with a risk of ionizing radiation, estimated GFR based on the endogenous markers creatinine or cystatin C, either alone or in combination, is easier and more commonly used [12]. In children, there are several GFR equations that include height, weight, age and gender [13], e.g. the bedside Schwartz equation and the quadratic formula by Gao, both based on serum creatinine, and the Zappitelli equation, based on both serum creatinine and cystatin C [14–16].

Creatinine, the waste product from creatine and phosphocreatine, found mainly in skeletal muscle, is freely filtered through the glomerulus and secreted through the proximal tubules. Its value as a renal function marker is hampered by biological and analytical variations. There is considerable variation in serum levels due to differences in height, muscle mass, gender and diet [17], the analytical methods show substantial variability, and there is no standardized test method [18]. *Cystatin C* is produced at a constant rate in all cells, and excreted by glomerular filtration followed by catabolism in the tubular cells. As it is less affected by height, weight, muscle mass and diet than creatinin, its plasma concentration has been proposed as a better renal function marker for pediatric patients [19]. *Symmetric dimethylarginine (SDMA)* is a methylated arginine metabolite produced in all nucleated cells and excreted in the kidneys. The plasma level is correlated to inulin clearance in children, and thus, SDMA has been put forward to serve as an endogenous marker of renal function [20].

We investigated renal function by creatinine, cystatin C, SDMA and estimated GFR in two groups of 11 year old children; term-born children with appropriate birth weight (BW) for gestational age (AGA) and children born extremely preterm (EP) or with an extremely low birth weight (ELBW). Our hypothesis was that being born EP/ELBW and especially SGA within the EP/ELBW group, was associated with decreased renal function.

Methods

Study population

As part of a prospective national study [21], a cohort of infants born EP, i.e. gestational age (GA) <28 weeks, or with ELBW, i.e. BW <1000 grams, within Western Norway Health Authority in 1999 and 2000, were prospectively recruited for follow-up at birth. The health region serves a population of approximately 1.1 million, and all the infants were initially treated at the university hospitals in Bergen or Stavanger.

The children were invited for follow-up at 11 years of age. For each EP/ELBW participant, the next-born child of the same gender with GA >37 weeks and BW >3000 grams was identified from birth protocols in the maternity ward and invited as a control. If the parents declined, the next-born child was approached until a match was obtained.

Neonatal data were obtained from compulsory notifications to the Medical Birth Registry of Norway and from registration forms developed for the study and completed by neonatologists during the stay in the neonatal intensive care nursery, and by pediatricians and parents during follow-up [22]. Small for gestational age (SGA) was defined as BW <10th percentile for GA according to Norwegian growth curves [23].

The Regional Committee on Medical Research Ethics granted ethical approval of the protocol, and the mothers gave written, informed consent.

Data collection and biochemical analysis

At 11 years of age (in 2010–2011), the children were assessed at the University Hospitals in Bergen or Stavanger, according to place of birth. Height, weight, waist circumference, triceps and scapular skinfolds were measured. Body mass index (BMI: weight/height²) and subscapular to triceps skinfold ratio (STR) were calculated as estimates of body fat deposition and truncal fat mass [24]. Systolic and diastolic blood pressures (BP) were measured three times by an electronic device (GE Critikon Dinamap XL vital signs) and a mean value was calculated.

Blood samples were obtained by antecubital venipuncture and collected into EDTA Vacutainer Tubes (Becton Dickinson) for separation of plasma and in Vacutainer Tubes without additives (Becton Dickinson) for separation of serum. Blood samples for preparation of EDTA-plasma were placed in ice water, and plasma was separated within 4 hours. The samples were stored at –80°C until analysis.

Renal function markers included plasma creatinine, cystatin C, symmetric dimethylarginine (SDMA) and estimated GFR. Plasma levels of creatinine and SDMA were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) [25]. Creatinine measured by LC-MS/MS is about 10% lower than values obtained with a creatinine iminohydrolase procedure. The difference may be related to the higher specificity of and less interference for the LC-MS/MS method. The lower limit of detection (LOD) of creatinine in this assay is 0.25 µmol/L, within-day CV is 3–5%, and between-day CV is 2–6% (www.bevital.no). Plasma levels of cystatin C were measured using immuno-MALDI-MS, with a LOD of 0.003 µg/mL and a within-day CV of 4–6% (www.bevital.no) [26].

Estimated GFR was based on the bedside Schwartz equation, i.e. $0.413 \times \text{height} / \text{Creatinine}$, the Zappitelli equation, i.e. $(507.76 \times e^{0.003 \times \text{height}}) / (\text{Cystatin C}^{0.635} \times \text{Creatinine}^{0.547})$ [15, 16] and the new quadratic formula by Gao et al, i.e. $0.68 \times (\text{height (cm)} / \text{serum Creatinine (mg/dl)}) - 0.0008 \times (\text{height (cm)} / \text{serum Creatinine (mg/dl)})^2 + 0.48 \times \text{age (years)} - (21.53 \text{ in males or } 25.68 \text{ in females})$ [14].

Statistical analysis

Results are presented as means, standard deviations and 95% confidence intervals (CIs) or as medians and interquartile range (IQR) and compared by ANOVA/Student's t-test or Kruskal Wallis test. Differences in categorical variables were tested by Chi-Square tests. Trends for differences according to birth status (from term-born via preterm AGA to preterm SGA) were assessed by linear regression. The Spearman's test was used to calculate correlations, and multiple linear regressions to assess renal function after adjusting for birth status and growth parameters (AGA vs. SGA).

The SPSS statistical package (version 23) was used for the statistical analyses and two-sided p-values < 0.05 were considered statistically significant.

Results

Demographics (Table 1)

Fifty-seven eligible EP/ELBW children were examined at a mean age of 11.4 (SD 0.4) years (Table 1). The GA ranged from 24 to 31 weeks and BW from 450 to 1250 grams; 46 (81%) were EP, 49 (86%) were ELBW. Twenty (35%) were born SGA; their mean BW was 200 grams lower than for those born AGA (p<0.001) despite a 2 weeks higher mean GA (p<0.001). Blood for assessment of renal function was successfully obtained from 50/57 EP/ELBW and from 45/54 control children, with no differences as regards other measurements between those with or without blood samples.

Table 1. Demographic characteristics in the term-born and preterm-born children (n = 111).

Variables	Term-born AGA children (n = 54)	Preterm-born children		P value	P for trend††
		AGA (n = 37)	SGA (n = 20)		
At birth					
Weight, g	3701 (3582, 3819)	918 (867, 968)	724 (657, 791)	<0.001*	
Gestational age, wks		26.1 (25.7, 26.5)	28.0 (27.2, 28.7)	<0.001*	
Male sex, n (%)	29 (54%)	16 (43%)	13 (65%)	0.27**	
At study inclusion					
Age, y	11.7 (11.2–12.0)	11.4 (11.1–11.8)	11.3 (11.0–11.8)	0.08†	
Weight, kg	41.3 (38.9, 43.6)	40.1 (37.5, 42.6)	36.2 (32.0, 40.3)	0.07*	0.03
Height, cm	151.5 (149.2, 153.8)	149.2 (146.7, 151.8)	142.6 (139.7, 145.4)	<0.001*	<0.001
BMI (kg/m ²)	17.8 (17.1, 18.6)	17.8 (17.1, 18.6)	17.6 (16.2, 19.1)	0.95*	0.81
Waist circumference, cm	66.3 (64.1, 68.5)	65.9 (63.1, 68.7)	65.1 (61.0, 69.3)	0.86*	0.59
Triceps skinfold, mm	12.3 (11.2, 13.5)	11.7 (10.2, 13.2)	11.1 (9.1, 13.1)	0.53*	0.26
Subscapular skinfold, mm	8.6 (7.3, 9.8)	8.7 (7.3, 10.1)	9.1 (7.0, 11.2)	0.11*	0.66
Subscapular to triceps ratio	0.70 (0.64, 0.76)	0.76 (0.69, 0.82)	0.82 (0.68, 0.97)	0.10*	0.03
Systolic BP, mm HG	109.1 (106.7, 111.4)	113.0 (109.9, 116.2)	110.4 (106.2, 114.6)	0.12*	0.28
Diastolic BP, mm HG	64.1 (62.1, 66.1)	64.8 (62.1, 67.4)	63.8 (59.9, 67.6)	0.97*	0.98

The results are presented as mean (95% CI), comparison by Anova test*, as number (%), comparison by Pearson Chi-Square test** and median and IQR, comparison by Kruskal Wallis test†. P for trend by linear regression††. AGA = appropriate birthweight for gestational age, SGA = small birthweight for gestational age.

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At 11 years mean height was lower in the EP/ELBW children, whereas mean weight and BMI were similar to that of the term controls. Within the EP/ELBW children, those born SGA were shorter, but their mean weight and BMI were similar to that of those born AGA. STR skinfold thickness increased from the term-born group through the preterm AGA and preterm SGA children (Table 1).

There were no differences in mean systolic or diastolic BP between term and preterm AGA or SGA children (Table 1). Systolic BP correlated positively with BMI, weight, waist circumference, subscapular skinfold and STR ($r > 0.22$, $p < 0.03$), but not with height, triceps skinfold or renal function parameters.

Renal function

All renal function parameters were inter-correlated (Table 2). The SDMA level increased and the estimated GFR decreased from the term-born group through the preterm AGA and preterm SGA groups, whereas there were no significant group differences for creatinine or cystatin C levels (Table 3).

After adjusting for age, gender, weight and height in a multiple linear regression model, there was an increase in plasma creatinine ($B = 2.1$, $p = 0.02$), cystatin C ($B = 0.04$, $p = 0.05$) and SDMA ($B = 0.03$, $p = 0.009$) and a reduction in GFR Schwartz ($B = -4.4$, $p = 0.02$), GFR Gao ($B = -2.8$, $p = 0.02$) and GFR Zappitelli ($B = -5.8$, $p = 0.007$) from the term-born through the preterm AGA and preterm SGA groups. The endogenous renal markers (including estimated GFR) did not correlate with systolic or diastolic BP ($P > 0.13$).

Discussion

At 11 years of age, children born EP/ELBW had impaired renal function compared to term born peers, as reflected in lower GFR and higher SDMA. Renal function was more impaired in children born preterm and SGA compared to those born preterm and AGA. Blood pressure was unrelated to GA, BW or SGA vs. AGA status, but systolic BP was positively associated with indices of increased fat mass.

Renal function in relation to prematurity, low birth weight and SGA

There is increasing awareness that adverse intrauterine conditions may lead to developmental programming causing non-communicable diseases later in life, a concept labeled ‘developmental origins of health and disease’ (DOHaD). For hypertension and renal disease, these issues may be related to adverse fetal events that modify the nephron number and/or function [27].

Table 2. Spearman correlation between renal function parameters in term-born and preterm-born children at 11 years (n = 95).

	Creatinine	Cystatin C	SDMA	GFR Schwartz	GFR Zappitelli
Cystatin C, $\mu\text{mol/L}$	0.33**				
SDMA, $\mu\text{mol/L}$	0.40*	0.39*			
GFR Schwartz	-0.88*	-0.28**	-0.41*		
GFR Gao	-0.85*	-0.28*	-0.41*	0.96*	0.65*
GFR Zappitelli	-0.68*	-0.89*	-0.50*	0.66*	

$P < 0.001^*$,

$P < 0.01^{**}$

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Table 3. Renal function parameters in the term-born and preterm-born children at 11 years (n = 95).

Renal function parameters*	Term-born AGA children (n = 45)	Preterm-born children		P*	P trend**	P†	P††
		AGA (n = 33)	SGA (n = 17)				
Creatinine, µmol/L	51.0 (49.2, 52.8)	51.6 (49.8, 53.5)	53.6 (49.5, 57.6)	0.34	0.17	0.31	0.37
Cystatin C, mg/L	0.86 (0.82, 0.90)	0.89 (0.84, 0.94)	0.91 (0.85, 0.98)	0.39	0.17	0.21	0.58
SDMA, µmol/L	0.55 (0.52, 0.57)	0.56 (0.53, 0.58)	0.61 (0.57, 0.66)	0.01	0.009	0.09	0.02
GFR Schwartz	110.0 (106.2, 113.7)	106.8 (103.3, 110.4)	99.0 (91.0, 106.9)	0.009	0.003	0.03	0.07
GFR Gao	105.6 (103.4, 107.8)	103.5 (101.4, 105.6)	98.4 (92.4, 104.4)	0.007	0.002	0.02	0.05
GFR Zappitelli	104.8 (100.3, 109.3)	101.2 (96.2, 106.3)	95.1 (89.7, 100.5)	0.055	0.017	0.05	0.13

The results are presented as mean (95% CI), comparison by Anova test* and P for trend by linear regression** and by Student's t-test between † term and preterm and between †† AGA and SGA preterms.

AGA = appropriate birthweight for gestational age, SGA = small birthweight for gestational age

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Different research groups have reported higher blood pressure or reduced renal function in groups of individuals born preterm and/or at a low birth weight [7–9], corresponding to our findings. However, these previous studies have examined adult populations in a retrospective manner, and based their sample selection on reported birth weight less than 2500 gram [7–9], and thus may not be comparable. In an unselected population, BW less than 2500 gram principally corresponds to being born moderately preterm and AGA, or being born SGA at term. Applying this inclusion criterion, it may thus be challenging to disentangle if outcomes relate to preterm birth *per se* or to an adverse intrauterine environment. Moreover, studies investigating cohorts born at different gestational ages may not be directly comparable. Fetal kidney development will have reached different developmental stages at birth and the mechanisms for reduced kidney function are likely to differ. Finally, some studies have investigated only males [7], or found the association only in males (Li), whereas the distribution of gender in our cohort was approximately as would be expected in a preterm born group of individuals.

The mechanisms linking preterm birth, fetal growth restriction and impaired renal function are poorly understood. Nephrogenesis begins around the ninth week of pregnancy and terminates around 36 weeks' gestation in term-born infants. More than 60% of adult nephrons are formed during the last two trimesters of pregnancy; thus, the number of nephrons correlates positively with GA at birth [28]. Nephrons have no re-generational ability if damaged, and must last a life-time. Preterm birth implies premature exposure to the haemodynamic transitions of birth, leading to the postnatal increase in systemic blood pressure and in renal blood flow, potentially impacting nephron development [29–33]. Preterm birth also implies exposure to a range of intensive care interventions that may have additional negative impact on nephron development and later renal function, such as prenatal steroids [34], the use of nephrotoxic drugs [35], exposure to infections and suboptimal nutrition. The association between prematurity and altered renal function may therefore be explained by both development of fewer nephrons after premature birth *per se*, as well as by abnormal nephrons that are formed post-natally, while the preterm infant is exposed to neonatal intensive care [28].

Fetal growth restriction *as such* may also result in lower numbers of nephrons in premature SGA infants, with the number of nephrons increasing by approximately 250,000 per kg birth-weight [33, 36]. A reduced number of nephrons is an important factor in the development of later kidney disease and hypertension [30], a risk that seems to be amplified in those born SGA [29, 31, 32].

Thus, the present study reinforces concerns expressed previously for those born *both* prematurely *and* SGA [37, 38]. The finding that children born preterm and SGA have poorer renal function than children born preterm and AGA, suggests that disadvantageous antenatal factors are likely to be involved in the causal chain, in addition to the preterm birth *as such*. Nevertheless, it is important to bear in mind that all markers of renal function were within published normal reference ranges [15, 16, 19, 39, 40] in all groups at 11 years of age, and therefore the long-term significance of the findings are unknown.

Hypertension in relation to prematurity, low birth weight and SGA

Hypertension is both a major cause and a result of chronic kidney disease. Both prematurity and LBW has been shown to increase the risk of later hypertension [41]. In meta-analyses, the mean systolic BP was 2.5 (95% CI: 1.7–3.3) mm Hg higher in subjects born preterm than at term [41] and 2.3 mm Hg higher in subjects with BW below 2500 g compared to those with a normal BW [42]. Since the heights of preterm born children of the present study were lower than their term-born peers, and BP values for children and adolescents rest on height percentiles, we expected they would have lower BP. In agreement with previous studies, we observed positive correlations between systolic BP and indices of body fat distribution [43]. However, despite an increased truncal fat mass, we found no difference in BP between preterm and term-born children. This may have been due to the limited size of the study.

Growth and body composition in relation to prematurity, low birth weight and SGA

Apart from height, growth parameters were similar in preterm and term-born children. The preterm SGA children had the shortest stature, but the highest subscapular to triceps skinfold ratio, suggesting a relatively higher truncal fat mass. Similar observations have been made in many [44–46], but not all [47] previous studies investigating these issues. In a recent large study on 11 year old Belarussian children, those who were born SGA were reported to be thinner and shorter, and with less fat than children born AGA; however, that study did not include children with a BW <2500 gram [47].

In line with the DohAD concept, most epidemiological studies suggest that being born SGA is associated with higher percentages of body fat and truncal obesity in later childhood and adulthood [44–46]. The causal pathway might have altered fetal programming linking restricted fetal growth, risk of the metabolic syndrome and chronic diseases in adulthood [46]. Our finding of impaired renal function in preterm SGA children fit this hypothesis.

Strengths and limitations of the study

This was a population-based study. It included three endogenous markers of renal function, including SDMA, which has not previously been evaluated in a preterm population. The attendance rate was high, and the recruitment of the control group followed a strict algorithm based on the ‘next-born-subject’ principle, minimizing risks of selection bias. The study design prescribed inclusion of all subjects born EP (GA < 28 weeks), but also those with ELBW (< 1000 gram) irrespective of GA. Thus, the results indicate that extreme prematurity, and in particular early intrauterine growth restriction, may be risk factors for early renal impairment

and related health consequences. However, the results do not necessarily generalize to all preterm-born children. The low number of participants is an obvious weakness, impacting statistical power and opening for type I as well as type II statistical errors, although the size of the study population is comparable to that of most follow-up studies on children born EP/ELBW. Lack of data on urine albuminuria, urine albumin-creatinine ratio or 24 h ambulatory blood pressure, represent additional weaknesses of the study.

Conclusion

Eleven year old EP/ELBW children, and in particular those born SGA, had poorer renal function than peers born at term. The findings indicate that being born preterm and SGA implies an increased risk of developing kidney disease later in life.

Author Contributions

Conceptualization: Maria Vollsæter, Thomas Halvorsen, Trond Markestad, Knut Øymar, Anne-Lise Bjørke-Monsen.

Data curation: Maria Vollsæter, Thomas Halvorsen, Trond Markestad, Knut Øymar, Anne-Lise Bjørke-Monsen.

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