Pediatric Nephrology
https://doi.org/10.1007/s00467-019-04255-1

ORIGINAL ARTICLE

Association of low birth weight and prematurity with clinical outcomes of childhood nephrotic syndrome: a prospective cohort study

Natalia Konstantelos[1,2] · Tonny Banh[1] · Viral Patel[2] · Jovanka Vasilevska-Ristovska[1] · Karlota Borges[1] · Neesha Hussain-Shamsy[2] · Damien Noone[2,3] · Diane Hebert[2,3] · Seetha Radhakrishnan[2,3] · Christoph P.B. Licht[2,3] · Valerie Langlois[2,3] · Rachel J. Pearl[2,3,5] · Rulan S. Parekh[1,2,3,4,6]

Received: 31 August 2018 / Revised: 11 January 2019 / Accepted: 29 March 2019

Abstract

Background Low birth weight (LBW)/prematurity have been proposed as risk factors for the development of kidney disease in adulthood. Whether there is an association between LBW/prematurity and poor renal outcomes in childhood onset nephrotic syndrome remains unknown.

Methods Children with nephrotic syndrome diagnosed between 1 and 18 years of age were followed prospectively from 1996 to 2016 at The Hospital for Sick Children ($N = 377$). LBW/prematurity was defined as birth weight < 2500 g or gestational age < 36 weeks. Normal birth weight (NBW) was defined as birth weight ≥ 2500 g. Measures evaluating clinical course of nephrotic syndrome include initial steroid-resistant nephrotic syndrome (SRNS), time to first relapse, and frequently relapsing nephrotic syndrome. Kaplan-Meier survival analysis, logistic regression, and Cox proportional hazards regression were used to determine the association of LBW/prematurity with clinical outcomes.

Results Median birth weights in LBW/premature ($n = 46$) and NBW ($n = 331$) children were 2098 g (interquartile range [IQR] 1700–2325 g) and 3317 g (IQR 2977–3685 g), respectively. Odds of having SRNS were 3.78 (95% confidence interval [CI] 1.28–11.21) times higher among LBW/premature children than NBW children. An 8% decrease in odds of developing SRNS was observed for every 100 g increase in birth weight (adjusted odds ratio [OR] 0.92; 95% CI 0.86–0.98). Median time to first relapse did not differ (hazard ratio [HR] 0.89; 95% CI 0.53–1.16).

Conclusions LBW/premature children were more likely to develop SRNS but did not have a difference in time to first relapse with NBW children. Understanding the impact and mechanism of birth weight and steroid-resistant disease needs further study.

Keywords Nephrotic syndrome · Low birth weight · Prematurity · Steroid resistant nephrotic syndrome · Time to first relapse

✉ Rulan S. Parekh
rulan.parekh@sickkids.ca

1 Child Health Evaluative Sciences, Research Institute, Hospital for Sick Children, 686 Bay St, Toronto, ON M5G 0A4, Canada

2 University of Toronto, 27 King's College Cir, Toronto, ON M5S 3H7, Canada

3 Division of Nephrology, Hospital for Sick Children, 555 University Ave, Toronto, ON M5G 1X8, Canada

4 University Health Network, 101 College St, Toronto, ON M5G 1L7, Canada

5 Department of Pediatrics, William Osler Health System, 101 Humber College Blvd, Etobicoke, ON M9V 1R8, Canada

6 Dalla Lana School of Public Health, University of Toronto, 155 College St, Toronto, ON M5T 3M7, Canada

Introduction

Nephrotic syndrome is characterized by massive proteinuria leading to hypoalbuminemia, hypercholesterolemia, and edema and is the most common kidney disease diagnosed in children [1, 2]. Genetic, as well as environmental factors contribute to the development of nephrotic syndrome [3]. Prognosis and clinical outcomes of nephrotic syndrome, however, are difficult to predict. In 1989, Barker and colleagues hypothesized that prenatal development can have an effect on health later in life, such as an increase in systolic blood pressure [4]. Most notably, they found an inverse association between birth weight and death from cardiovascular disease [5]. More recently, this phenomenon was expanded to kidney disease [6].

Published online: 11 April 2019

Birth weight is associated with the number of nephrons and glomeruli that develop [7]. Nephrogenesis occurs in utero and is completed at 34–36 weeks of gestation, with 60% of nephrons developing in the third trimester, leaving premature children at significant risk of incomplete kidney development [8]. In extremely preterm infants, nephrogenesis stops 40 days after birth [9]. Low birth weight (LBW) and prematurity are also risk factors for the development of high blood pressure, proteinuria, and reduction in the number of nephrons [10]. Notably, weight gain in the first 2 years of life has no impact on the severity of kidney disease, allowing the use of birth weight as a predictor of disease course [11]. Mechanistically, a reduction in nephron number leads to a decrease in glomerular filtration surface area, which results in an adaptive response to increase single nephron glomerular filtration rate [12]. This response subsequently increases the risk of developing kidney disease and renal injury because such hyperfiltration ultimately results in reduced glomerular filtration rate and functional renal reserve [10]. The effect of LBW and prematurity on incomplete kidney development in utero may explain the differences in outcomes among children with nephrotic syndrome.

Early evidence suggests that the perinatal environment has a role in determining the severity of the nephrotic syndrome as well as the response to steroids [11]. Previous studies looking at the effect of birth weight on outcomes of nephrotic syndrome have categorized birth weight as small for gestational age or intrauterine growth retardation; few have used the LBW criterion [11, 13–15]. These studies have examined the effect of birth weight and prematurity on the outcomes of nephrotic syndrome and found that children with lower birth weights had an aggravated course of nephrotic syndrome indicated by steroid resistance, steroid dependence, and frequent relapses in cohorts of approximately 40–60 children [11, 13–15]. These findings, however, need to be further validated in a larger cohort.

Our objective is to determine the association of LBW and prematurity with clinical outcomes of childhood nephrotic syndrome such as steroid resistance, time to first relapse, frequently relapsing nephrotic syndrome, and the development of a first relapse.

Methods

Study population

Children were enrolled in the study Insight into Nephrotic Syndrome: Investigating Genes, Health and Therapeutics (INSIGHT), a prospective cohort study [16]. Nephrotic syndrome was defined as proteinuria (≥ 40 mg/m^2/h or urine protein/creatinine ratio ≥ 200 mg/mL or 3+ protein on urine dipstick), hypoalbuminemia (< 25 g/L), and edema [1]. Our population included 423 children diagnosed with nephrotic syndrome between the ages of 1–18 and followed from January 1, 1996 to July 1, 2016 at the Hospital for Sick Children, Toronto. Children with congenital nephrotic syndrome, disease involving multiple organs, or secondary causes of nephrotic syndrome were excluded. The final cohort consisted of 377 children after excluding those with missing birth weight, diagnosis date, gestational age, or clinical data ($n = 46$). The study was approved by the Hospital for Sick Children's Research Ethics Board (ClinicalTrials.gov identifier NCT01605266). Data were obtained by medical chart review for outcomes and completion of parental self-reported questionnaires for birth-related information. Maternal smoking was defined as smoking cigarettes for more than 5 days in the last 3 months of pregnancy. The indication for biopsy was SRNS, suspecting other underlying disease, assessing calcineurin inhibitor toxicity, and if presentation occurred before the age of 1, or over the age of 12. Estimated glomerular filtration rate (eGFR) was calculated from patient height and serum creatinine values. For participants with a visit date prior to March 17, 2008, the Schwartz formula was used with a correction factor of 0.85 to account for differences in serum creatinine measurements at the Hospital for Sick Children as previously reported [17, 18]. For participants with a visit date on or after March 17, 2008, the modified Schwartz equation was used [18].

Low birth weight/premature birth

Low birth weight and/or prematurity was defined according to the World Health Organization as a child born weighing < 2500 g or born at a gestational age of < 36 weeks, a gestational age up to and including 35 weeks and 6/7 days of pregnancy [19]. Accordingly, children were considered to have normal birth weight (NBW) if they were born weighing ≥ 2500 g.

Outcomes in nephrotic syndrome

Several outcomes of nephrotic syndrome from the INSIGHT cohort were described previously [20]. Briefly, we defined a relapse as having ≥ 3.0 g/L of protein in urine for three consecutive days that requires use of steroids resulting in an increase in steroid dose. Complete remission was defined as no additional episodes of proteinuria requiring medical intervention after initial treatment. Time to first relapse was defined as the number of days from diagnosis to first relapse. Initial steroid-resistant nephrotic syndrome (SRNS) was defined as the initiation of a second-line medication during the initial steroid treatment. Frequently relapsing nephrotic syndrome (FRNS) was defined as ≥ 2 relapses within 6 months of diagnosis or ≥ 4 relapses in any 12-month period. FRNS at 12 months after diagnosis was evaluated in our study.

Statistical analysis

Baseline characteristics between the LBW/premature and NBW groups were described. A two-sample *t* test was used for normally distributed continuous variables, and a Wilcoxon-Mann-Whitney test for non-normal continuous variables. A χ^2 test was used for categorical variables. If assumptions of the χ^2 test were violated, Fisher's exact test was used.

We determined the association of LBW/prematurity relative to NBW with the occurrence of a first relapse, SRNS, and FRNS at 12 months using logistic regression. Kaplan-Meier survival analysis was used to compare time to first relapse between LBW/premature and NBW children. To determine the association of LBW/prematurity with the time to first relapse, Cox proportional hazards regression was used. Analyses were adjusted for ethnicity, gender, and maternal age at time of birth because previous studies identified potential confounding by these factors on the course of nephrotic syndrome [20–22].

Birth weight was further assessed as a continuous variable by determining the odds of developing SRNS per 100-g increase in birth weight using logistic regression. Differences were considered to be significant if $p \leq 0.05$. Statistical analysis was performed using STATA/SE 14.

Results

Baseline characteristics

The study cohort of 377 children primarily consisted of males (63.7%). There were 46 (12%) LBW/premature children with a median birth weight of 2098 g (interquartile range [IQR] 1700–2325), and those with NBW had a median birth weight of 3317 g (IQR 2977–3685) ($p < 0.01$; Table 1). There was a difference in gender between LBW/premature and NBW children. Prevalence of maternal smoking during pregnancy was significantly different between LBW/prematurity and NBW groups ($p < 0.05$). Age of diagnosis, age of enrollment, follow-up time, eGFR, and maternal age at time of birth did not differ between LBW/premature and NBW children.

Clinical outcomes

The median times to first relapse were 0.42 and 0.58 years for the LBW/premature and NBW groups, respectively. No significant differences in time to first relapse were found between LBW/premature and NBW children (log-rank $p = 0.5$; Fig. 1).

Children with LBW/prematurity had a *3.16-times higher odds of SRNS* (95% confidence interval [CI] 1.15–8.61) compared to NBW, which remained high, at 3.78 (95% CI 1.28–11.24), after adjustment (Table 2). LBW/premature children also had a higher odds ratio (1.57; 95% CI 0.67–3.67) of developing a relapse as compared to children with NBW, but statistical significance was not reached in either unadjusted or adjusted analyses. The odds of developing FRNS at 12 months among LBW/premature children was 0.47 times (95% CI 0.16–1.39) that of NBW children. LBW/prematurity was *not associated with time to first relapse* (HR 0.89; 95% CI 0.64–1.25) of LBW/premature children compared to NBW children.

In unadjusted analyses, each 100 g increase in birth weight was associated with 7% decrease in odds of SRNS (OR 0.93; 95% CI 0.88–0.99; $p < 0.05$). This association remained significant after adjusting for ethnicity, gender, and maternal age at time of birth (OR 0.92; 95% CI 0.86–0.98; $p < 0.05$) (Table 3).

Discussion

Children with nephrotic syndrome born with LBW/prematurity were almost *four times* more likely to have SRNS compared to NBW children. There was, however, no difference on time to first relapse observed among children with steroid sensitive disease. Furthermore, we demonstrated a significant inverse relationship between increasing birth weight and the odds of having SRNS.

Steroid responsiveness is a major determinant of the long-term prognosis of childhood nephrotic syndrome [2, 23]. SRNS is the second most frequent cause of end-stage renal disease in the first 20 years of life, and an especially important outcome of nephrotic syndrome due to the lifelong repercussions of disease [24]. Our results with respect to SRNS are consistent with those found in the literature, with multiple studies demonstrating that there are differences in steroid response among children with varying birth weights [11, 13, 14, 25]. However, these studies were inconsistent with the World Health Organization in their definitions of LBW and have used small for gestational age and intrauterine growth retardation as parameters [19]. Furthermore, varying definitions of SRNS were used. In one study, which defined LBW as birth weight below the 10th percentile for gestational age and had a cohort size of 55 children, with only 4 of these children being LBW, it was found that LBW children were more likely to have SRNS than NBW children [25]. Furthermore, a study defining intrauterine growth retardation as birth weight below the 10th percentile for gestational age and a cohort of 56 children, 8 having intrauterine growth retardation found an increase in the incidence of SRNS in IUGR children [14]. In accordance with these studies, another study using small for gestational age as a parameter, defined as birth weight below or equal to the 7th percentile, and a cohort size of 62 children with only 5 of these children being small for gestational age, found that children born small for gestational age were more likely to be steroid resistant [11].

Table 1 Baseline characteristics and outcomes of 377 children with nephrotic syndrome born with normal and low birth weight/premature births (1996–2016)

	Low birth weight/premature[a] ($n = 46$)	Normal birth weight[b] ($n = 331$)	p value
Baseline characteristics	n (%)/mean ± standard deviation / median [interquartile range]		
Male	20 (43.5)	220 (66.5)	0.02*
Birth weight (grams)	2097.8 [1700.0–2325.6]	3316.8 [2976.7–3685.4]	0.001*
Age at diagnosis, years	3.6 [2.5–5.4]	3.6 [2.7–5.8]	0.3
Age of enrollment, years	7.9 [5.2–10.4]	8.2 [4.6–13.9]	0.6
Follow-up time, years	5.6 [2.5–8.07]	4.9 [2.02–6.9]	0.2
eGFR at initial visit[c] (mL/min/1.73 m^2)	181.9 [135.1–191.8]	167.0 [143.7–185.3]	0.3
Maternal age at time of birth, years	29.9 [27–33]	29.9 [26–34]	0.9
Maternal smoking during pregnancy[d]	≤ 5	9 (3.8)	0.01*
Ethnicity			0.01*
European	< 10	112 (33.8)	
South Asian	23 (50.0)	105 (31.7)	
East/South East Asian	< 5	26 (7.8)	
Other [e]	15 (32.6)	88 (26.6)	

[a] Low birth weight includes children born < 2500 g or born < 36 weeks of gestation

[b] Normal birth weight includes children born ≥ 2500 g

[c] Estimated glomerular filtration rate in mL/min/1.73 m^2 at the patient's initial visit

[d] Maternal smoking at least 1 cigarette > 5 days during the last 3 months of pregnancy

[e] Other includes Mixed ($n = 59$), West Indian or Caribbean ($n = 19$), Middle Eastern ($n = 11$), African ($n = 6$), Aboriginal ($n \leq 5$), Mexican or South or Central American ($n \leq 5$), Unknown ($n \leq 5$)

*$p \leq 0.05$

Reasons for differences in steroid response in LBW/premature children are not well understood. The immune system mediates the relapses seen in nephrotic syndrome and is targeted to mitigate disease [26]. Most notably, steroids decreased CD4 and CD8 T cell counts in children with nephrotic syndrome compared to those not treated with steroids [27]. Furthermore, in a study comparing small for gestational age infants, and infants born appropriate for gestational age,

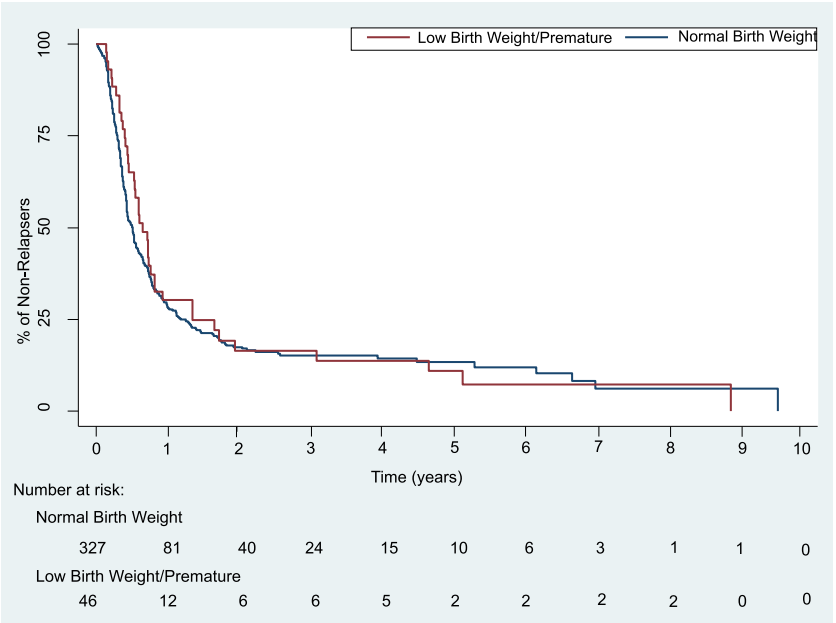

Fig. 1 Initial time to first relapse by birth weight. Kaplan-Meier survival analysis for initial time to first relapse in low birth weight/premature and normal birth weight children. Median initial times to first relapse are 0.42 (approximately 5 months) and 0.58 years (approximately 7 months), respectively, and log-rank p value = 0.51

Table 2 Association of low birth weight/prematurity with first relapse, initial steroid resistance, frequently relapsing nephrotic syndrome at 12 months after initial treatment, and time to first relapse among 377 children diagnosed with nephrotic syndrome (1996–2016)

		SRNS[a]	First relapse[b]	FRNS (at 12 Months)[c]	Time to First Relapse[d]
Normal birth weight ($n = 331$)	Events, *n*	15	258	55	257
	Odds/hazard ratio	*Ref.*	*Ref.*	*Ref.*	*Ref.*
Low birth weight/premature ($n = 46$)	Events, *n*	6	39	≤ 5	40
	Odds/hazard ratio	3.16	1.57	0.47	0.89
	95% confidence interval	1.15–8.61	0.67–3.67	0.16–1.39	0.64–1.25
	Adjusted odds/hazard ratio[e]	3.78	1.43	0.35	0.79
	95% confidence interval	1.28–11.24	0.59–3.42	0.10–1.18	0.53–1.16

[a] SRNS is initial steroid resistant nephrotic syndrome

[b] First relapse refers to the patient ever developing a relapse (≥ 3.0 g/L of protein in urine for 3 consecutive days that requires the use of steroids resulting in an increased steroid dose)

[c] FRNS is frequently relapsing nephrotic syndrome

[d] Time to first relapse is the number of days from diagnosis to the patient's first relapse (having ≥ 3.0 g/L of protein in urine for three consecutive days that requires the use of steroids resulting in an increased steroid dose)

[e] Odds and hazard ratios are adjusted for ethnicity, gender, and maternal age at time of birth

small for gestational age children had a lower overall percent of CD4, and a lower CD4 to CD8 ratio, further demonstrating that birth weight may affect immunological profiles [28]. Preterm infants also have altered gut microbiota, which have a role in the induction of regulatory T cells [29, 30]. Birth weight has also been considered a factor in the disruption of gut microbiota [31]. Gut dysbiosis has been found to be more prevalent in children exhibiting relapses than those in remission [30, 32]. Dysfunction of the immune system, specifically regulatory T cells and their role in the development and progression of idiopathic nephrotic syndrome, has been proposed in a theoretical framework [32]. However, the effects of the microbiome on the immune system are only speculative.

We find that there is no significant difference between LBW/premature and NBW children with respect to time to first relapse. This result is consistent with a study that reported no difference in this parameter in children with IUGR and those appropriate for gestational age [14]. Another study found that LBW children had 129 days to first relapse of which was not significantly different from that in NBW children of 163 days. However, these results were determined from sample sizes of less than 60 children [25]. Our cohort of 377 participants gave comparable results with respect to time to first relapse.

The prevalence of maternal smoking was found to differ between LBW/premature children and NBW children. This is in accordance with the US Department of Health and Human Services, which concluded that there is a casaul relationship between maternal smoking and fetal growth restriction [33]. Possible epigenetic mechanisms may explain this phenomenon as smoking affects mitochondrial DNA methylation which results in altered ATP production and placental function, leading to differences in birth weight [34].

The strengths of our study include a large, a multi-ethnic cohort recruited across a large urban area. We used a common treatment protocol that eliminates clinical treatment provided to patients as a potential confounding factor [20]. Limitations of this study are parental self-reported birth weights and the lack of kidney size measurement at birth. Nonetheless, studies have concluded that parental self-reported birth weights are valid to use for both clinical as well as epidemiological purposes, with findings proving the accuracy of parental self-

Table 3 Birth weight (per 100 g) evaluated as a continuous variable for 377 children diagnosed with nephrotic syndrome from 1996 to 2016 with respect to initial steroid resistance

	Events, *n*	Odds Ratio	95% confidence interval	*p* value	Adjusted odds ratio[b]	95% confidence interval	*p* value
SRNS[a]	21	0.93	0.88–0.99	0.04*	0.92	0.86–0.98	0.01*

[a] SRNS is initial steroid resistant nephrotic syndrome

[b] Odds ratio is adjusted for ethnicity, gender, and maternal age at time of birth

* $p \leq 0.05$

reported birth weights [35]. Studies have found that parental recalled birth weights were correct within 50 g of the hospital records 75% of the time, and gestational ages were correct within 1 week, with findings irrespective of parental socioeconomic status, age, or education level [35, 36]. Furthermore, studies have found a linear relationship between nephron number and birth weight between the 10th to 90th percentiles for gestational age as well as a direct correlation between birth weight and number and size of glomeruli [7, 37]. The evidence from these studies allows us to use birth weight as a reliable indicator of renal development to explain differences in clinical outcomes. In future studies, sensitivity analyses using IUGR and very low birth weight could be studied. However, we are not powered to complete these analyses. Additionally, we were not powered to compare ethnic differences by birth weight and prematurity; nonetheless, we report differences in birth weight based on ethnicity (Table 1). In a previous study at our center, incidence and outcomes of nephrotic syndrome differed by ethnicity; however, this study included historical data where parental report on birth information was not available [20]. Future studies should also consider the gestational age in weeks for a more specific measure of the clinical outcomes of nephrotic syndrome.

Low birth weight and prematurity are important clinical factors to consider in the history of children with nephrotic syndrome. We conclude that LBW/premature children with nephrotic syndrome are more likely to be steroid resistant, and thus should be followed closely to ensure prompt assessment and suitable treatment. LBW/prematurity can be used by physicians as indicator for increased risk of steroid resistance. These steroid-resistant children could be treated with ACE inhibitors or calcineurin inhibitors sooner, as demonstrated in randomized control trials to decrease proteinuria and increase the likelihood of complete or partial remission in SRNS compared to treatment with cyclophosphamide or placebo [26]. However, these trials did not specify if these children were LBW/premature—further studies are needed to verify the effects of ACE and calcineurin inhibitors in this specific patient group. Long-term health risks of LBW/prematurity in children with chronic kidney disease need to be studied further.

Acknowledgements We thank the participants and their families for their time and effort, as well as the nurses and staff from the Nephrology Clinic at the Hospital for Sick Children and William Osler Health System—Brampton Civic Hospital and Peel Memorial Centre. We also thank Richard Child for his advice and insight into the electronic patient record.

Authors' contributions Research idea and study design: RP; CPBL DN, DH; SR; RJP; and VL; data acquisition: VP, TB, NHS, JVR, and KB; manuscript drafting: NK; statistical analysis: NK and TB; figure preparation: NK and TB; supervision: RP. Each author contributed important intellectual content during manuscript revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy and integrity of any portion of the work are appropriately investigated and resolved.

Funding This study was funded by the Hospital for Sick Children Research Institute and Physicians' Services Incorporated.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

References

1. Samuel S, Bitzan M, Zappitelli M, Dart A, Mammen C, Pinsk M, Cybulsky A, Walsh M, Knoll G, Hladunewich M, Bargman J, Reich H, Humar A, Muirhead N (2014) Canadian Society of Nephrology Commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis: management of nephrotic syndrome in children. Am J Kidney Dis 63:354–362
2. Eddy AA, Symons JM (2003) Nephrotic syndrome in childhood. Lancet 362:629–639
3. Akchurin ORK (2015) Genetic causes of proteinuria and nephrotic syndrome: impact on podocyte pathobiology. Pediatr Nephrol 30: 221–223
4. Barker D, Bull A, Osmond C, Simmonds S (1990) Fetal and placental size and risk of hypertension in adult life. BMJ 301:259–262
5. Barker D, Winter P, Osmond C, Margetts B, Simmonds S (1989) Weight in infancy and death from ischaemic heart disease. Lancet 2: 577–580
6. Lackland DT, Bendall HE, Osmond C, Egan BM, Barker DJ (2000) Low birth weights contribute to high rates of early-onset chronic renal failure in the southeastern United States. Arch Intern Med 160:1472–1476
7. Hughson M, Farris AB III, Douglas-Denton R, Hoy WE, Bertram JF (2003) Glomerular number and size in autopsy kidneys: the relationship to birth weight. Kidney Int 63:2113–2122
8. Boubred F, Saint-Faust M, Buffat C, Ligi I, Grandvuillemin I, Simeoni U (2013) Developmental origins of chronic renal disease: an integrative hypothesis. Int J Nephrol
9. Rodriguez MM, Gomez AH, Albitbol CL, Chandar JJ, Duara S, Zillerelo GE (2004) Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. Pediatr Dev Pathol 7:17–25
10. Luyckx VA, Bertram JF, Brenner BM, Fall C, Hoy WE, Ozanne SE, Vikse BE (2013) Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. Lancet 382:273–283
11. Plank C, Ostreicher I, Dittrich K, Waldherr R, Voigt M, Amann K, Rascher W, Dötsch J (2007) Low birth weight, but not postnatal weight gain, aggravates the course of nephrotic syndrome. Pediatr Nephrol 22:1881–1889
12. Brenner BM, Garcia DL, Anderson S (1988) Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens 1:335–347
13. Zidar N, Avgustin Cavić M, Kenda R, Ferluga D (1998) Unfavorable course of minimal change nephrotic syndrome in children with intrauterine growth retardation. Kidney Int 54:1320–1323

14. Na YW, Yang HJ, Choi JH, Yoo KH, Hong YS, Lee JW, Kim SK (2002) Effect of intrauterine growth retardation on the progression of nephrotic syndrome. Am J Nephrol 22:463–467
15. Sheu JN, Chen JH (2001) Minimal change nephrotic syndrome in children with intrauterine growth retardation. Am J Kidney Dis 37: 909–914
16. Hussain N, Zello JA, Vasilevska-Ristovska J, Banh TM, Patel VP, Patel P, Battiston CD, Herbert D, Licht CP, Piscone TD, Parekh RS (2013) The rationale and design of insight into nephrotic syndrome: investigating genes, health and therapeutics (INSIGHT): a prospective cohort study of childhood nephrotic syndrome. BMC Nephrol:14
17. Schwartz GJ, Haycock B, Edelmann CM Jr, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from Blody length and plasma. Creatinine Pediatrics 58:259–263
18. Alkandari O, Hebert D, Langlois V, Robinson LA, Parekh RS (2017) Validation of serum creatinine-based formulae in pediatric renal transplant patients. Pediatr Res 86:1000–10006
19. World Health Organization (2010) International statistical classification of diseases and health related problems, tenth revision. In: Organization WH (ed), Geneva, Switzerland
20. Banh TH, Hussain-Shamsy N, Patel V, Vasilevska-Ristovska J, Borges K, Sibbald C, Lipszyc D, Brooke J, Geary D, Langlois V, Reddon M, Pearl R, Levin L, Piekut M, Licht CP, Radhakrishnan S, Aitken-Menezes K, Harvey E, Hebert D, Piscione TD, Parekh RS (2016) Ethnic differences in incidence and outcomes of childhood nephrotic syndrome. Clin J Am Soc Nephrol 11:1760–1768
21. Ingulii E, Tejani A (1991) Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children. Pediatr Nephrol 5:393–397
22. Franke I, Aydin M, Llamas Lopez CE, Kurylowicz L, Ganschow R, Lentze M, Born M (2017) The incidence of the nephrotic syndrome in childhood in Germany. Clin Exp Nephrol
23. Webb NJ, Lewis MA, Iqbal J, Smart PJ, Lendon M, Postlethwaite RJ (1996) Childhood steroid-sensitive nephrotic syndrome: does the histology matter? Am J Kidney Dis 27:484–488
24. Smith JM, Stablein DM, Munoz R, Hebert D, McDonald R (2007) Contributions of the transplant registry: the 2006 annual report of the north American pediatric renal trials and collaborative studies (NAPRTCS). Pediatr Transplant 11:366–373
25. Teeninga NSM, Bökenkamp A, Delemarre-van de Waal HA, van Wijk JA (2008) Influence of low birth weight on minimal change nephrotic syndrome in children, including a meta-analysis. Nephrol Dial Transplant 23:1615–1620
26. Hodson EM, Wong SC, Willis NS, Craig JC (2016) Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database Syst Rev
27. Baris HE, Baris S, Karakoc-Aydiner E, Gokce I, Yildiz N, Cicekkoku D, Ogulur I, Ozen A, Alpay H, Barlan I (2016) The effect of systemic corticosteroids on the innate and adaptive immune system in children with steroid responsive nephrotic syndrome. Eur J Pediatr 175:685–693
28. Chatrath R, Saili A, Jain M, Dutta AK (1997) Immune status of full-term small-for-gestational age neonates in India. J Trop Pediatr 43: 345–348
29. Ruiz L, Moles L, Gueimonde M, Rodruiguez JM (2016) Perinatal microbiomes' influence on preterm birth and preterms' health: influencing factors and modulation strategies. J Pediatr Gastroenterol Nutr 63:e193–e203
30. Tsuji S, Suruda C, Hashiyada M, Kimata T, Yamanouchi S, Kitao T, Kino J, Akane A, Kaneko K (2018) Gut microbiota dysbiosis in children with relapsing idiopathic nephrotic syndrome. Am J Nephrol 47:164–170
31. Unger U, Stintzi A, Shah P, Mack D, O'Connor DL (2015) Gut microbiota of the very-low-birth-weight infant. Pediatr Res 77: 205–213
32. Kaneko K, Tsuji S, Kimata T (2017) Role of gut microbiota in idiopathic nephrotic syndrome in children. Med Hypotheses 108: 35–37
33. US Department of Health and Human Services (2004) The health consequences of smoking: a report of the surgeon general. In: US Department of Health and Human Services (ed). US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health,, USA
34. Armstrong D, Green B, Blair B, Guerin D, Litzky J, Chavan N, Pearson K, Marsit C (2016) Maternal smoking during pregnancy is associated with mitochondiral DNA methylation. Environ Epigenetics 2
35. Seidman D, Slater P, Ever-Hadani P, Gale R (1987) Accuracy of mothers' recall of birthweight and gestational age. Br J Obstet Gynaecol 94:731–735
36. O'Sullivan JJ, Pearce MS, Parker L (2000) Parental recall of birth weight: how accurate is it? Arch Dis Child 82:202–203
37. Mañalich R, Reyes L, Herrera M, Melendi C, Fundora I (2000) Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. Kidney Int 58:770–773