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ORIGINAL ARTICLE

Impact of childhood nephrotic syndrome on obesity and growth: a prospective cohort study

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Abstract

Background Children with nephrotic syndrome are at risk of obesity and growth impairment from repeated steroid treatment. However, incidence and risk factors for obesity and short stature remain uncertain, which is a barrier to preventative care. Our aim was to determine risk, timing, and predictors of obesity and short stature among children with nephrotic syndrome.

Methods We evaluated obesity and longitudinal growth among children (1–18 years) enrolled in Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics. We included children with nephrotic syndrome diagnosed between 1996–2019 from the Greater Toronto Area, Canada, excluding congenital or secondary nephrotic syndrome. Primary outcomes were obesity (body mass index Z-score $\geq +2$) and short stature (height Z-score ≤ -2). We evaluated prevalence of obesity and short stature at enrolment (< 1-year from diagnosis) and incidence during follow-up. Cox proportional hazards models determined the association between nephrotic syndrome classification and new-onset obesity and short stature.

Results We included 531 children with nephrotic syndrome (30% frequently relapsing by 1-year). At enrolment, obesity prevalence was 23.5%, 51.8% were overweight, and 4.9% had short stature. Cumulative incidence of new-onset obesity and short stature over median 4.1-year follow-up was 17.7% and 3.3% respectively. Children with frequently relapsing or steroid dependent nephrotic syndrome within 1-year of diagnosis were at increased risk of new-onset short stature (unadjusted hazard ratio 3.99, 95%CI 1.26–12.62) but not obesity (adjusted hazard ratio 1.56, 95%CI 0.95–2.56). Children with ≥ 7 and ≥ 15 total relapses were more likely to develop obesity and short stature, respectively.

Conclusions Obesity is common among children with nephrotic syndrome early after diagnosis. Although short stature was uncommon overall, children with frequently relapsing or steroid dependent disease are at increased risk of developing short stature. Effective relapse prevention may reduce steroid toxicity and the risk of developing obesity or short stature.

Keywords Nephrotic syndrome · Childhood · Pediatric · Growth · Short stature · Obesity

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Abbreviations

INSIGHT	Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics study
KDIGO	Kidney Disease Improving Global Outcomes
BMI	Body mass index
WHO	World Health Organization
CI	Confidence interval
IQR	Interquartile range
IR	Incidence rate
HR	Hazard ratio

Introduction

Nephrotic syndrome is one of the most common childhood kidney diseases and is associated with significant disease- and treatment-related morbidity. Incidence of childhood nephrotic syndrome is 2–7/100,000 children per year [1–3]. The introduction of steroid treatment in the mid-twentieth century considerably improved disease-related morbidity and mortality, but increased treatment-related complications. Approximately 90% of children have steroid sensitive nephrotic syndrome, but most relapse and receive repeated steroid treatments [1, 2]. One-third develop frequently relapsing or steroid dependent nephrotic syndrome, which is associated with increased steroid complications, morbidity, and reduced quality of life [1, 4–6].

Obesity and growth impairment are associated with high-dose, prolonged, and repeated steroid treatment [7]. Chronic steroid exposure predisposes to obesity by increasing appetite, promoting lipogenesis, and altering lipid and glucose metabolism [8]. Steroids adversely impact linear growth by inhibiting osteoblastogenesis, increasing bone resorption, inhibiting pulsatile growth hormone secretion, and inhibiting growth plate chondrocytes [7]. Since frequently relapsing patients often receive high-dose steroids for relapses, they are at considerable risk of both obesity and growth impairment. Several studies have evaluated obesity and linear growth among children with nephrotic syndrome, with conflicting results [9–11]. Comparability between these studies is limited by significant heterogeneity in study design, populations, and growth outcomes measured. Most have small sample sizes and are cross-sectional or have short follow-up duration. Therefore, the long-term incidence and risk factors associated with obesity and short stature in childhood nephrotic syndrome remain uncertain. To address this, we evaluated longitudinal growth patterns in a large, prospective cohort of Canadian childhood nephrotic syndrome patients.

Methods

Study design

We analyzed data from the *Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics* (INSIGHT) study. INSIGHT is a longitudinal cohort of children diagnosed with nephrotic syndrome from 1996 onwards, which has enrolled participants from the Greater Toronto and Hamilton Area. Institutional research ethics board approved all INSIGHT clinical sites. Nephrotic syndrome is defined by standardized Kidney Disease Improving Global Outcomes (KDIGO) criteria (i.e., the presence of proteinuria ($\geq$40 mg/m^2/hour, urine protein/creatinine ratio $\geq$ 200 mg/mmol, or 3 + protein on urine dipstick), hypoalbuminemia ($\leq$25 g/L), and edema) [12]. At INSIGHT study centers, the standard prednisone protocol for initial presentation was 60 mg/m^2 daily for 6 weeks, followed by 40 mg/m^2 alternate days for 6 weeks, and a 4-week taper off prednisone (cumulative steroid dose = 3620 mg/m^2). The standard relapse protocol was 60 mg/m^2 daily until five consecutive days of remission, then 60 mg/m^2 alternate days for eight days, and further taper by 10 mg/m^2 every 8 days until off prednisone (approximately 7-week taper; cumulative steroid dose ~ 1440 mg/m^2, assuming 10 days from prednisone initiation to start of taper). INSIGHT participants have detailed baseline evaluations of sociodemographic and clinical characteristics with self-reported questionnaires, and undergo annual follow-up for five years or until clinic discharge.

Population

We included all INSIGHT participants (1–18 years old) who were diagnosed with nephrotic syndrome and had an initial clinic visit within 1 year of diagnosis from 1996 to 2019. Children were excluded if they had genetic or secondary nephrotic syndrome (e.g., lupus nephritis); were < 1 yr at diagnosis (i.e., congenital nephrotic syndrome); or had biopsy-proven membranous nephropathy or membranoproliferative glomerulonephritis. At INSIGHT centers during the study period, children were typically treated for their initial presentation with prednisone 60 mg/m^2/day for 6 weeks, then 40 mg/m^2 alternate days for 6 weeks, then a 4-week prednisone taper. Relapses were treated with prednisone 60 mg/m^2/day until five consecutive days of remission, then a 6-week alternate day prednisone taper. Steroid-sparing medications were typically initiated as soon as a child met criteria for frequently relapsing, steroid dependent, or steroid resistant disease. Cyclophosphamide and calcineurin inhibitors were the most common first-line medications used.

Growth outcomes

Height, weight, and body mass index (BMI) were recorded at each clinic visit. Height and BMI Z-scores were calculated using the 'z-scorer' package (version 0.3.1) for R Statistical Software based on World Health Organization (WHO) growth references [13]. A Z-score ("standard deviation

score") measures the number of standard deviations above or below the population mean. Primary outcomes were: 1) new-onset obesity, using the WHO definition [14] (BMI Z-score $\geq +2$) at any follow-up visit, among children who were non-obese (BMI Z-score $< +2$) at their initial visit, and 2) new-onset short stature, using the WHO definition (height Z-score $\leq$ -2) at any follow-up visit, among children who did not have short stature (height Z-score > -2) at their initial visit. For the primary outcomes, time zero was the date of nephrotic syndrome diagnosis. Secondary outcomes included the prevalence at the initial visit (within 1 year of nephrotic syndrome diagnosis) and the last clinic visit (before transition to adult care or loss-to-follow-up) of obesity, overweight status (BMI Z-score $\geq +1$), and short stature. We also evaluated BMI and height Z-scores longitudinally (i.e., change in Z-score per year) throughout follow-up.

Exposure and comparator

Our key exposure was nephrotic syndrome classification within 1-year of diagnosis, using KDIGO definitions [12]. Frequently relapsing nephrotic syndrome was defined as ≥ 2 relapses within the first 6 months or ≥ 4 relapses within 1 year. Steroid dependent nephrotic syndrome was defined as two consecutive relapses during or within 14 days of stopping steroid treatment. Steroid resistant nephrotic syndrome was defined as the receipt of a steroid-sparing immunosuppressive medication prior to completion of the initial steroid course (within 12 weeks for children diagnosed prior to 2002 or 16 weeks for children diagnosed after 2002).

Baseline characteristics

Demographic and birth characteristics assessed were age at diagnosis, sex, self-reported ethnicity (classified using Statistics Canada defined categories) [3], immigration status, birth weight, gestational age, delivery method, parental education, and total family income. Clinical characteristics included diagnosis year, clinical center, initial steroid treatment duration, time to first relapse, total relapse count, steroid-sparing medication use, and biopsy histopathology. Each covariate was selected based on theoretical or reported associations with obesity and short stature in childhood nephrotic syndrome. Baseline covariates with $\geq 15\%$ missing data were excluded from regression models [15]. For baseline covariates with $< 15\%$ missing data (birthweight, term delivery, parental education, ethnicity, and age at diagnosis), multiple imputation by chained equations was used [15, 16].

Statistical analysis

All statistical analyses were performed using R Statistical Software (version 4.2.2, Vienna, Austria). We compared baseline characteristics using descriptive statistics, stratified by nephrotic syndrome classification within 1 year of diagnosis. Univariable testing was performed for all primary and secondary outcomes by exposure status, using distribution-appropriate tests. Changes in the prevalence of obesity and short stature among the overall cohort from the initial to last clinic visit were analyzed by McNemar's test for paired data. Mean BMI and height Z-scores were plotted by years since diagnosis with corresponding 95% confidence intervals (CI).

We then performed time-to-event analysis for new-onset obesity and short stature by Kaplan–Meier method, compared using log rank testing. These analyses were restricted to children who did not have obesity or short stature at their initial clinic visit (within 1 year of nephrotic syndrome diagnosis), respectively. In all analyses, censoring occurred at last study follow-up visit or administrative censoring in Dec 2019 (i.e., the end of data availability). We evaluated the association between nephrotic syndrome classification within 1 year of diagnosis (categorized as frequently relapsing or steroid dependent nephrotic syndrome vs. infrequent or no relapses) and time to new-onset obesity and short stature using Cox proportional hazards regressions over longitudinal follow-up. First, univariable Cox models were used to evaluate unadjusted associations between nephrotic syndrome classification and new-onset obesity and short stature. Next, the Cox model for new-onset obesity was adjusted for the following baseline covariates, which were specified a priori: age at diagnosis, sex, ethnicity, parental education, and birthweight. Relevant model assumptions were verified, including proportional hazards, lack of influential observations, and overspecification. We performed additional sensitivity analysis accounting for clustering by clinical center in our multivariable new-onset obesity model, using a generalized estimating equation with robust variance estimation. We also evaluated the association between nephrotic syndrome classification (categorized as frequently relapsing, steroid dependent, or steroid resistant nephrotic syndrome vs. infrequent or no relapses) and time to new-onset obesity and short stature. Multivariable Cox regression was infeasible for short stature, due to the low number of events. We performed analyses with univariable and multivariable adjusted generalized linear regression models to evaluate the association between nephrotic syndrome classification and annualized change of BMI and height Z-scores from the initial to last clinic visit. Finally, we performed a sensitivity analysis restricting the population to children with an initial clinic visit between 6–12 months after nephrotic syndrome diagnosis to account for possible residual edema from initial presentation and restricting to children with an initial clinic visit between 0–1 month after nephrotic syndrome diagnosis (i.e., before steroid-induced obesity or short stature could develop).

Results

Patient characteristics

We included 531 children with an incident diagnosis of nephrotic syndrome, who had a median time from nephrotic syndrome diagnosis to initial visit of 12 days (interquartile range (IQR) 3–81 days). Frequently relapsing or steroid dependent nephrotic syndrome was diagnosed in 160 (30.1%) within 1 year of diagnosis and 33 (6.2%) had initial steroid resistance (Table 1). On average, children with frequently relapsing or steroid dependent nephrotic syndrome were younger at diagnosis. Median duration of follow-up was 4.1 years (IQR 2.2–7.4) overall.

Weight and obesity outcomes

At the initial clinic visit, 125 children (23.5%) were obese and 275 (51.8%) were overweight (Table 2). Among children who were non-obese at their initial visit, 69 (17.7%) developed new-onset obesity throughout follow-up (incidence rate (IR) 3.6 per 100 person-years). Among initially non-overweight children, 75 (31.3%) became overweight throughout follow-up (IR 6.5 per 100 person-years). Children with frequently relapsing or steroid dependent nephrotic syndrome within 1 year of diagnosis were at higher risk of developing new-onset obesity (adjusted hazard ratio (HR) 1.56, 95%CI 0.95–2.56; Table 3 and Fig. 1a), although this was not statistically significant ($p = 0.08$) after adjusting for age at diagnosis, sex, ethnicity (European vs. other), parental education (less than high school completion vs. other), and birthweight. There was no substantial change in these results when including children with steroid resistant nephrotic syndrome (Supplemental Table 1). After adjusting for clustering by clinical center, frequently relapsing or steroid dependent nephrotic syndrome classification was significantly associated with new-onset obesity (adjusted HR 1.56, 95%CI 1.15–2.12, $p = 0.005$). Children who developed new-onset obesity had a higher total relapse count than those who did not (Fig. 2a). Children who experienced ≥ 7 total relapses (approximate cumulative steroid dose > 13 g/m^2) had a significantly higher incidence of new-onset obesity (33.3%) vs. those with < 7 total relapses (10.8%), $p < 0.001$ (chi-squared test). At the last follow-up visit, 91 children (17.3%) remained obese and 218 (41.5%) remained overweight. Obesity prevalence decreased significantly from the initial to last clinic visit ($p = 0.002$, McNemar's test).

Among the overall cohort, mean and median BMI Z-scores were + 1.20 (SD 1.30) and + 1.11 (IQR 0.40–1.96) at the initial visit and + 0.69 (SD 1.37) and + 0.68 (IQR -0.26–1.66) at last follow-up. Mean BMI Z-scores were significantly higher among children with frequently relapsing, steroid dependent, or steroid resistant nephrotic syndrome at the initial and last visits (Table 2). The mean annual change in BMI Z-score was -0.17 (SD 0.55) overall, decreasing similarly in all nephrotic syndrome classification groups. BMI Z-scores decreased over 2–3 years after nephrotic syndrome diagnosis (Fig. 3), before subsequently increasing. Frequently relapsing or steroid dependent nephrotic syndrome classification within 1 year of diagnosis was not significantly associated with annual change in BMI Z-score (adjusted estimate + 0.06, 95% CI -0.05 to + 0.16, $p = 0.32$, Fig. 4). Other factors associated with change in BMI Z-score are reported in Supplemental Table 2.

Linear growth outcomes

At the initial study visit, 26 children (4.9%) had short stature (Table 2). Among children who did not have short stature at their initial visit, 16 (3.3%) developed new-onset short stature throughout follow-up (IR 0.65 per 100 person-years). Children with frequently relapsing, or steroid dependent nephrotic syndrome had a higher cumulative incidence of short stature (unadjusted HR 3.99, 95%CI 1.26–12.62, $p = 0.02$; Table 3 and Fig. 1b). There was no substantial change in these results when including children with steroid resistant nephrotic syndrome (Supplemental Table 1). Children who developed new-onset short stature had a higher total relapse count than those who did not (Fig. 2b). Children who experienced ≥ 15 total relapses (approximate cumulative steroid dose > 25 g/m^2) had a significantly higher incidence of new-onset short stature (13.4%) vs. those with < 15 total relapses (1.7%), $p < 0.001$ (Fisher's exact test). Twenty children (3.8%) remained having short stature at their last follow-up visit. Short stature prevalence did not change significantly from the initial to last visit ($p = 0.29$).

Mean and median height Z-score were -0.07 (SD 1.17) and -0.02 (IQR -0.80–0.66) at the initial visit and + 0.13 (SD 1.13) and + 0.18 (IQR -0.53–0.91) at last follow-up. The mean annual change in height Z-score was + 0.06 (SD 0.37) overall and there was a significant difference between nephrotic syndrome classification groups (Table 2). Children with steroid resistant nephrotic syndrome had a negative annual change in height Z-score (mean -0.04, SD 0.46). Overall, height Z-scores increased within the first five years after diagnosis, before subsequently decreasing (Fig. 3). Frequently relapsing or steroid dependent nephrotic syndrome classification within 1-year of diagnosis was not significantly associated with annual change in height Z-score (adjusted estimate -0.06, 95%CI -0.14–0.01, $p = 0.09$, Fig. 4). Other factors associated with change in height Z-score are reported in Supplemental Table 3.

Table 1 Characteristics of INSIGHT participants from 1996 to 2019; stratified by nephrotic syndrome classification within 1-year of diagnosis

Covariate	No or infrequent relapses by 1-year ($n=338$)	FRNS/SDNS by 1-year ($n=160$)	Initial SRNS ($n=33$)
Age at diagnosis, mean years (SD)	5.4 (3.8)	4.5 (3.3)	6.0 (4.9)
Female sex, *n* (%)	127 (37.6)	50 (31.2)	13 (39.4)
Ethnicity, *n* (%)			
European	82 (25.7)	47 (30.3)	11 (34.4)
South Asian	112 (35.1)	48 (31.0)	10 (31.2)
Other Asian	42 (13.2)	20 (12.9)	4 (12.5)
Mixed/other	83 (26.0)	40 (25.8)	7 (21.9)
Birthweight, mean kg (SD)	3.1 (0.6)	3.2 (0.6)	2.9 (0.9)
Term delivery (≥ 36 weeks' gestation), *n* (%)	271 (87.1)	130 (86.7)	23 (74.2)
Vaginal delivery, *n* (%)	221 (65.4)	106 (66.3%)	17 (51.5)
Parental education, *n* (%)			
Elementary	22 (6.9)	10 (6.5)	4 (12.5)
High school	131 (41.3)	68 (44.2)	13 (40.6)
Undergraduate	88 (27.8)	47 (30.5)	10 (31.2)
Graduate	76 (24.0)	29 (18.8)	5 (15.6)
Total annual family income, *n* (%)			
< $50,000	72 (21.3)	34 (21.2)	4 (12.1)
$50,000 – 100,000	69 (20.4)	34 (21.2)	12 (36.4)
> $100,000	88 (26.0)	33 (20.6)	8 (24.2)
Unknown	109 (32.2)	59 (36.9)	9 (27.3)
Diagnosis year, *n* (%)			
1996–2005	49 (14.5)	46 (28.7)	6 (18.2)
2006–2010	73 (21.6)	43 (26.9)	10 (30.3)
2011–2015	132 (39.1)	38 (23.8)	13 (39.4)
2016–2019	84 (24.9)	33 (20.6)	4 (12.1)
Clinical center (SickKids), *n* (%)	249 (73.7)	136 (85.0)	24 (72.7)
Initial steroid treatment duration, *n* (%)			
< 8 weeks	10 (3.1)	19 (12.2)	4 (12.1)
8–16 weeks	203 (62.1)	83 (53.2)	4 (12.1)
> 16 weeks	85 (26.0)	45 (28.8)	18 (54.5)
Unknown	29 (8.9)	9 (5.8)	7 (21.2)
Time to first relapse, mean days (SD)	301 (283)	106 (54)	500 (467)
Total number of relapses, median (IQR)	3 (0–6)	8 (5–16)	0 (0–3)
Any steroid-sparing medication use, *n* (%)	110 (32.5)	144 (90.0)	33 (100.0)
Kidney biopsy performed, *n* (%)			
No	269 (79.6)	68 (42.5)	1 (3.0)
Yes	69 (20.4)	92 (57.5)	32 (97.0)
Biopsy pathology, *n* (%)			
FSGS	25 (7.4)	12 (7.5)	13 (39.4)
MCD	32 (9.5)	68 (42.5)	15 (45.5)
Other	12 (3.6)	12 (7.5)	4 (12.1)
Follow-up duration, median years (IQR)	3.7 (2.0–6.3)	5.6 (2.9–9.9)	4.3 (2.4–8.0)
Age at last follow-up, median (IQR)	9.3 (6.5–13.7)	10.2 (7.3–15.8)	14.5 (7.1–17.2)

FRNS Frequently relapsing nephrotic syndrome; *SDNS* Steroid dependent nephrotic syndrome; *SRNS* Steroid resistant nephrotic syndrome; *FSGS* Focal segmental glomerulosclerosis; *MCD* Minimal change disease

Frequently relapsing and steroid dependent nephrotic syndrome were classified within 1-year of diagnosis. Steroid resistant nephrotic syndrome was defined as resistance to the initial steroid treatment course after nephrotic syndrome diagnosis

Table 2 Obesity and height outcomes at the initial study visit, throughout study follow-up, and at the last study visit; stratified by nephrotic syndrome classification within 1-year of diagnosis

Outcome	Overall ($n=531$)	No or infrequent relapses by 1-year ($n=338$)	FRNS or SDNS by 1-year ($n=160$)	Initial SRNS ($n=33$)
Initial study visit				
Prevalent obesity at initial clinic visit, *n* (%)	125/531 (23.5)	59/338 (17.5)	51/160 (31.9)	15/33 (45.5)
Prevalent overweight at initial clinic visit, *n* (%)	275/531 (51.8)	166/338 (49.1)	89/160 (55.6)	20/33 (60.6)
Prevalent short stature at initial clinic visit, *n* (%)	26/531 (4.9)	15/338 (4.4)	8/160 (5.0)	3/33 (9.1)
Throughout study follow-up (median 4.1 years overall)				
New-onset obesity, *n* (%)	69/390 (17.7)	39/267 (14.6)	27/106 (25.5)	3/17 (17.7)
New-onset overweight, *n* (%)	75/240 (31.3)	43/160 (26.9)	25/68 (36.8)	7/12 (58.3)
New-onset short stature, *n* (%)	16/488 (3.3)	4/310 (1.3)	11/149 (7.4)	1/29 (3.5)
Last study visit				
Prevalent obesity at last clinic visit, *n* (%)	91/526 (17.3)	46/333 (13.8)	36/160 (22.5)	9/33 (27.3)
Prevalent overweight at last clinic visit, *n* (%)	218/526 (41.4)	126/333 (37.8)	72/160 (45.0)	20/33 (60.6)
Prevalent short stature at last clinic visit, *n* (%)	20/525 (3.8)	8/332 (2.4)	10/160 (6.3)	2/33 (6.1)

FRNS Frequently relapsing nephrotic syndrome; *SDNS* Steroid dependent nephrotic syndrome; *SRNS* Steroid resistant nephrotic syndrome; *BMI* Body mass index

Obesity, overweight status, and short stature were defined as BMI Z-score ≥ +2, BMI Z-score ≥ +1, and height Z-score ≤ -2, respectively. Prevalent obesity, overweight status, and short stature were both measured at the initial clinic visit (within 1-year of nephrotic syndrome diagnosis) and the last study visit. New-onset obesity, overweight status, and short stature analyses were restricted to individuals without prevalent obesity, overweight, or short stature (or missing BMI or height data) at the initial clinic visit

Table 3 Association of nephrotic syndrome classification within 1-year of diagnosis with new-onset obesity, new-onset short stature, and annual change in BMI and height Z-scores

Outcomes	No or infrequent relapses ($n=338$)	FRNS or SDNS ($n=160$)	*p*-value
New-onset obesity [a]			
HR (95% CI)	Ref	1.60 (0.98–2.61)	0.06
aHR* (95% CI)	Ref	1.56 (0.95–2.56)	0.08
New-onset short stature [a]			
HR (95% CI)	Ref	3.99 (1.26–12.62)	0.02
aHR (95% CI)	- [c]	-	-
Annual change in BMI Z-score throughout follow-up [b]			
Estimate (95% CI)	Ref	+0.04 (-0.07 to 0.14)	0.49
Adjusted estimate* (95% CI)	Ref	+0.06 (-0.05 to 0.16)	0.32
Annual change in height Z-score throughout follow-up [b]			
Estimate (95% CI)	Ref	-0.07 (-0.14 to 0.01)	0.07
Adjusted estimate* (95% CI)	Ref	-0.06 (-0.14 to 0.01)	0.09

Ref: reference group for the analysis (by row), *FRNS* Frequently relapsing nephrotic syndrome; *SDNS* Steroid dependent nephrotic syndrome

[*] Adjusted for age at diagnosis, sex, ethnicity (European vs. other), parental education (less than high school completion vs. other), and birthweight

[a] Time to new-onset obesity and short stature by Cox proportional hazards models

[b] Annual change in BMI and height Z-scores throughout follow-up by generalized linear model

[c] Multivariable adjusted analysis was not performed for time to new-onset short stature due to the small number of events

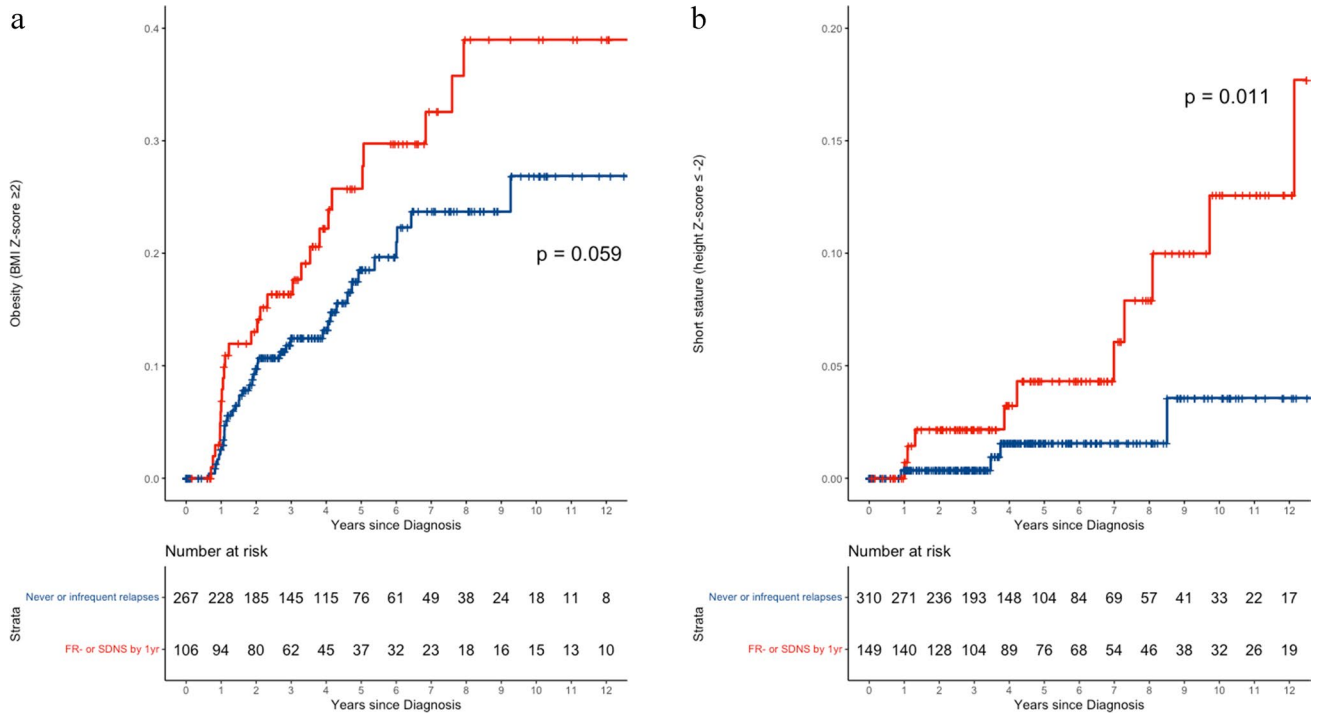


Fig. 1 Cumulative incidence of **a** new-onset obesity and **b** new-onset short stature. New-onset obesity (Fig. 1a) was defined using the WHO definition (BMI Z-score ≥ +2) at any study follow-up visit, among children who were non-obese (BMI Z-score < +2) at their initial visit. New-onset short stature (Fig. 1b) was also defined using the WHO definition (height Z-score ≤ -2) at any study follow-up visit, among children who did not have short stature (height Z-score > -2) at their initial visit. Children were classified as frequently relapsing (FR-) or steroid dependent (SD-) nephrotic syndrome within 1-year of diagnosis (red line) vs. never or infrequent relapses within 1-year of diagnosis (blue line). Children with steroid resistant nephrotic syndrome were excluded from this analysis. Children were censored at the time of loss to study follow-up or Dec 31, 2019 (administrative censoring)

Sensitivity analyses

Prevalence of obesity and short stature did not change substantially when restricting the cohort to children with an initial clinic visit between 0–1 month or 6–12 months after nephrotic syndrome diagnosis (Supplemental Table 4).

Discussion

Growth impairment and obesity are commonly reported side effects of systemic steroid treatment but have not been well-characterized longitudinally among children with nephrotic syndrome. Within one year from diagnosis, approximately half of children were overweight, one-quarter were obese, and less than 5% of children had short stature. Over median 4.1 years of follow-up, 18% went on to develop new-onset obesity and 3% new-onset short stature. However, the overall prevalence of obesity and BMI Z-scores decreased, and short stature and height Z-scores were relatively unchanged over the course of follow-up. This suggests that longitudinal changes in linear growth and BMI in childhood nephrotic syndrome are generally favourable. Children with frequently relapsing or steroid dependent nephrotic syndrome are at significantly higher risk of developing new-onset short stature, compared to those who never or infrequently relapse.

Prior growth and obesity studies in childhood nephrotic syndrome have reported conflicting results. Obesity is common among children with nephrotic syndrome and may be pre-existing at diagnosis or develop early in the disease course after steroid treatment [10, 17]. The reported prevalence of obesity varies significantly, ranging from 2–30% of cases [10, 17]. In a previous cross-sectional study of 96 patients with childhood nephrotic syndrome and 186 healthy controls, children with nephrotic syndrome had a significantly higher odds of obesity [9], especially those with recent steroid exposure within 6 months, higher maternal BMI, females, and non-Black race. Other studies have reported that obesity prevalence in children with nephrotic syndrome is similar to the general population [18–20]. Among children aged 5–17 years in Canada, the reported prevalence of obesity was 10.1% and overweight was 17.4% in 2019 [21]. We found that the prevalence of being obese or overweight within 1 year of nephrotic syndrome diagnosis and at the end of study follow-up were both approximately double the

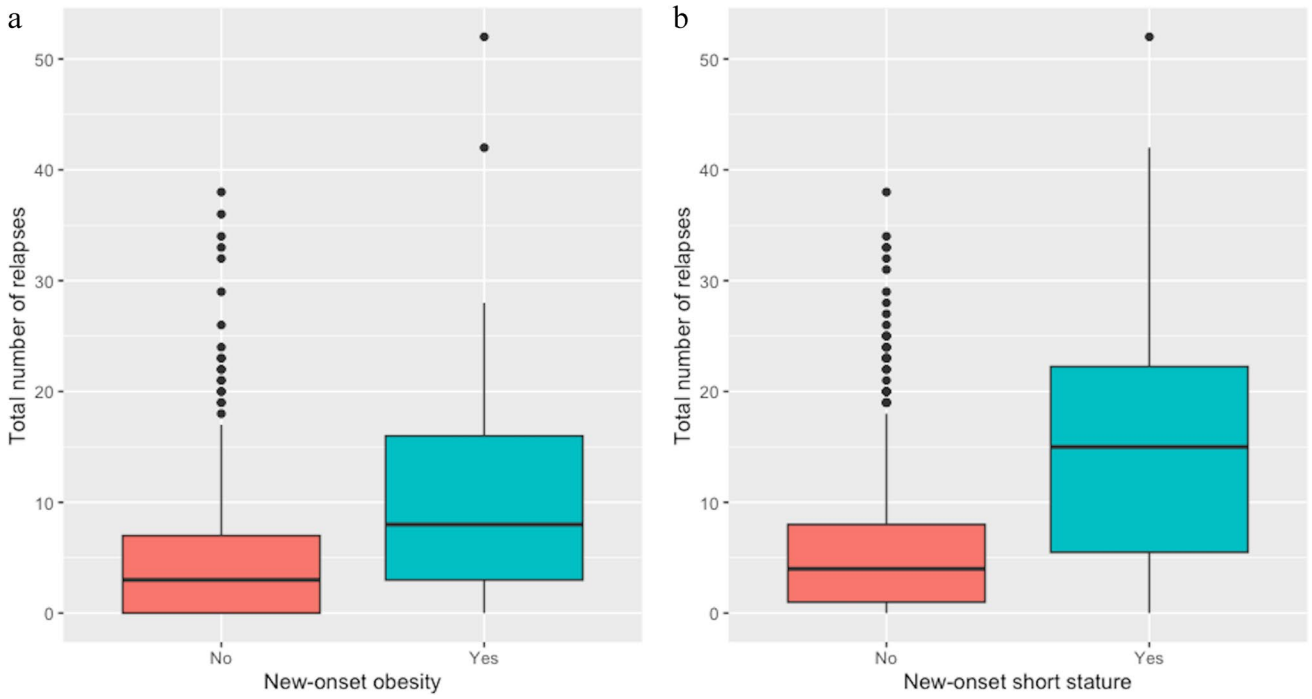
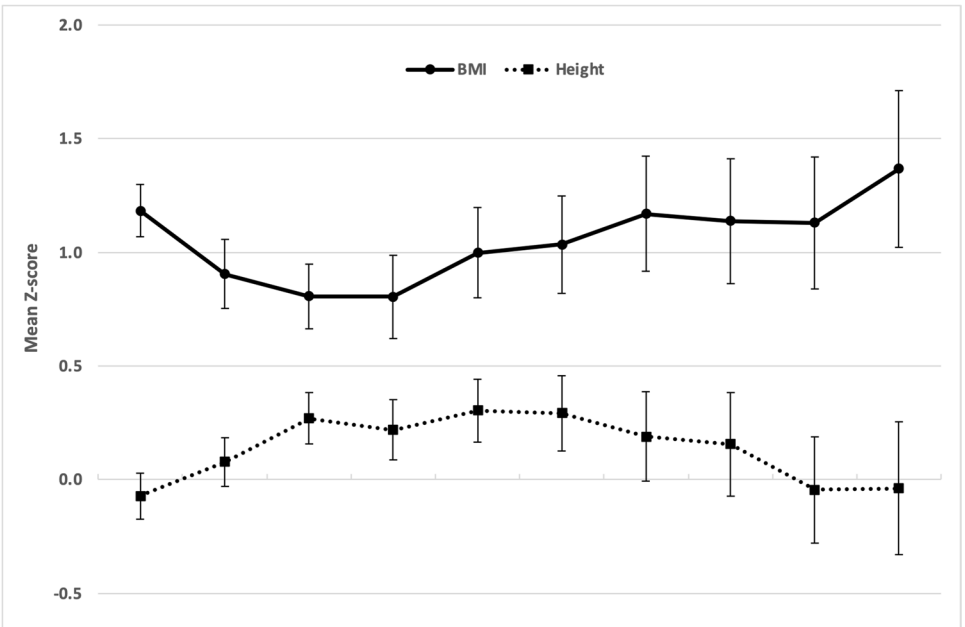


Fig. 2 Total number of relapses by **a** new-onset obesity and **b** new-onset short stature status. The total number of relapses was significantly higher in children that developed new-onset obesity or short stature. The mean total number of relapses was 10.7 in children that developed new-onset obesity and 5.3 in those that did not ($p < 0.001$). The mean total number of relapses was 17.6 in children that developed new-onset short stature and 5.9 in those that did not ($p = 0.008$)



Years since Dx	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10
N =	514	375	341	270	225	161	129	115	99	74

Fig. 3 Mean BMI and height Z-scores among INSIGHT participants from 1996–2019, by years since nephrotic syndrome diagnosis. Error bars represent 95% confidence interval around the mean. BMI Z-scores are represented by the solid line, height Z-scores are represented by the dashed line. "*N* =" represents the number of children with BMI and height Z-score data, by the number of years since nephrotic syndrome diagnosis ("Years since Dx")

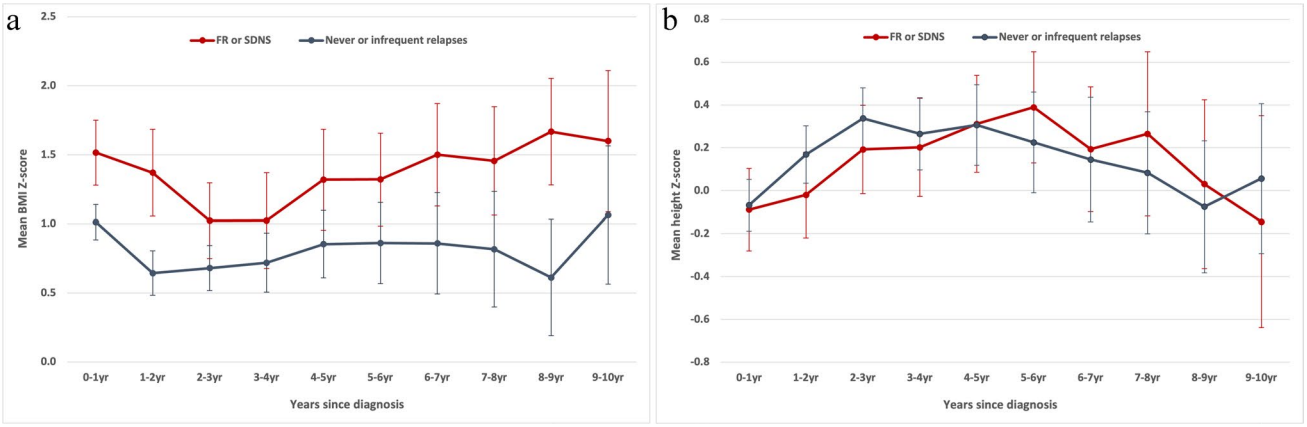


Fig. 4 Mean **a** BMI and **b** height Z-scores among INSIGHT participants from 1996–2019, by years since nephrotic syndrome diagnosis among children with no or infrequent relapses vs. frequent relapses (FR-) or steroid dependence (SD-) within 1-year of diagnosis. Error bars represent 95% confidence interval around the mean. BMI Z-scores are represented by the solid line, height Z-scores are represented by the dashed line

national average. However, we also found that mean BMI Z-scores improved overall within the first 2–3 years after nephrotic syndrome diagnosis, which may reflect normalization of weight after discontinuing steroids and resolution of edema from their initial presentation. Repeated steroid exposures may contribute to the subsequent increase in BMI Z-scores over later follow-up.

Several prior small studies have found that height Z-scores decrease after childhood nephrotic syndrome diagnosis [18, 22–24]. Mean final adult height Z-score is reported to be -0.2 to -0.8 [18, 19, 22, 24, 25], and short stature prevalence ranges from 0–16% in long-term cohort studies [10, 18–20, 26]. Among 56 Italian frequently relapsing nephrotic syndrome patients, the change in height Z-score from diagnosis to adulthood was -0.92 and 13% had short stature as adults [22]. They report that high cumulative steroid exposure and early age of diagnosis (< 3.5 years) were significant predictors of growth impairment. Other studies have reported normal linear growth and final adult height among children with nephrotic syndrome [19, 27, 28]. Two British longitudinal cohorts found that height velocity remains constant or increases over mean 3–5-year follow-up [11, 28]. In the second study of 265 children with nephrotic syndrome, 3.8% had short stature and 24% had obesity at last follow-up [11]. They found no differences in height or BMI change by age at diagnosis, sex, steroid sensitivity, or steroid dose. Similarly, we found that height and BMI Z-scores both improved throughout follow-up among the overall cohort, suggesting that changes in growth outcomes after nephrotic syndrome diagnosis are generally favourable. However, height Z-scores increased to a smaller degree for children with frequently relapsing or steroid dependent nephrotic syndrome and decreased for steroid resistant children. In our study, height Z-scores increased over the first five years after nephrotic syndrome diagnosis, which could reflect catch-up growth after initial steroid discontinuation and improved nutritional status. Prior studies have demonstrated catch-up growth after steroids discontinuation in nephrotic syndrome [29].

Finally, we evaluated the association between nephrotic syndrome classification within 1 year and new-onset obesity and short stature. Prior studies have not found consistent associations between obesity and cumulative steroid exposure or relapse frequency [18–20, 25]. Cumulative steroid exposure has previously been associated with linear growth impairment, although relapse frequency has not [18, 19, 22, 28–31]. Rituximab treatment results in decreases of cumulative steroid dose leading to improvements in height and BMI Z-scores [32, 33]. We could not evaluate the direct association between cumulative steroid dose and growth outcomes due to missing data on total steroid treatment duration. Instead, relapse count was used as a proxy measure of cumulative steroid exposure. In our study, we found that children with frequently relapsing or steroid dependent nephrotic syndrome were at increased risk of developing short stature. New-onset obesity was also more common in this group, although not statistically significant. These children may have been treated with other medications (e.g., calcineurin inhibitors) that increase the risk of obesity.

Our study has several strengths, including a large sample size, longitudinal growth parameter measurements, differentiation of prevalent vs. new-onset outcomes, and data on several key covariates for adjusted analyses. This facilitated evaluation of the prevalence, incidence, and the association between nephrotic syndrome classification with adverse growth outcomes. Our diverse childhood nephrotic syndrome cohort from multiple Ontario sites also increases generalizability. However, there are inherent limitations. Median age at last study follow-up

was 9.7 years, limiting comparability to studies reporting final adult height or obesity prevalence. Nevertheless, longitudinal data allowed precision in outcomes and trends in Z-scores over time. We lacked parental height, weight, or BMI data, preventing evaluation of predicted height or inclusion of these potential confounders. We also lacked data on pubertal timing, which could influence longitudinal growth patterns. However, the median age of the cohort at diagnosis was 3.7 years (IQR 2.8–6.4), so this data predominantly reflects pre-pubertal growth.

Conclusion

In a large, prospective longitudinal cohort study of children with nephrotic syndrome, incidence of new-onset obesity was 18% and new-onset short stature was 3% over median 4 years follow-up. Height and BMI Z-scores improved overall within the first 3–5 years after nephrotic syndrome diagnosis. The prevalence of obesity and being overweight at baseline (within 1 year of nephrotic syndrome diagnosis) were 24% and 52% respectively, which is twice that of the general pediatric population in Canada. This is concerning, given future cardiovascular and metabolic health risks associated with obesity. Those with frequent relapses and steroid dependence were also at increased risk of developing short stature during follow-up. Effective relapse prevention and steroid minimization is important as we follow children longitudinally to improve growth outcomes.

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Author contributions Cal H Robinson conceptualized and designed the study, performed data analysis, drafted the initial manuscript, and revised the manuscript. Nowrin Aman, Tonny Banh, Alisha Parikh, Veronique Rowley, and Jovanka Vasilevska-Ristovska collected data, assisted with data analysis and interpretation, and critically reviewed and revised the manuscript. Josefina Brooke, Rahul Chanchlani, Vaneet Dhillon, Valerie Langlois, Leo Levin, Christoph Licht, Ashlene McKay, Damien Noone, Rachel Pearl, Seetha Radhakrishnan, and Chia Wei Teoh advised on study design and critically reviewed and revised the manuscript. Rulan S Parekh advised on conceptualization and design of the study, assisted with data interpretation, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability Research supporting data are not available for public sharing. Individual investigators can connect with Drs Parekh and Robinson for potential collaborations.

Declarations

Conflict of interest The authors have no conflicts of interest relevant to this article to disclose.

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