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## Cardiovascular disease risk among children with focal segmental glomerulosclerosis: A report from the Chronic Kidney Disease in Children Study

Christine B Sethna<sup>1</sup>, Derek K. Ng<sup>2</sup>, Shuai Jiang<sup>2</sup>, Jeff Saland<sup>3</sup>, Bradley A. Warady<sup>4</sup>, Susan Furth<sup>5</sup>, and Kevin E. Meyers<sup>5</sup>

<sup>1</sup>Division of Pediatric Nephrology, Cohen Children's Medical Center of New York, New Hyde Park, NY;

<sup>2</sup>Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;

<sup>3</sup>Division of Pediatric Nephrology Mt. Sinai Medical Center, New York, New York,

<sup>4</sup>Division of Pediatric Nephrology, Children's Mercy Kansas City, Kansas City,

<sup>5</sup>Division of Pediatric Nephrology, Children's Hospital of Philadelphia, Philadelphia

### Abstract

**Background:** The aims were to compare the cardiovascular disease (CVD) risk among children with chronic kidney disease (CKD) secondary to focal segmental glomerulosclerosis (FSGS) with the CVD risk of children with CKD due to other diagnoses.

**Methods:** Casual blood pressure (BP), ambulatory blood pressure monitoring (APBM), echocardiogram, lipids, carotid intima medial thickness (cIMT) and uric acid obtained from participants in the Chronic Kidney Disease in Children (CKiD) cohort were analyzed longitudinally. Seventy-nine children with FSGS (FSGS-CKD) were compared to 196 children with non-FSGS glomerular disease (GDO-CKD) and 616 children with non-glomerular disease (NG-CKD).

**Results:** At baseline, FSGS-CKD (median 14 years) had ambulatory hypertension (24.6%), masked hypertension (46.2%), left ventricular hypertrophy (LVH) (26.3%) and dyslipidemia (60.0%). In adjusted models, FSGS-CKD had higher systolic BP z-score (0.52 vs 0.11 and 0.23,  $p=0.002$  and  $0.02$ ), triglycerides (133 vs 109 and 102 mg/dl,  $p=0.007$  and  $<0.001$ ) and non-high density lipoprotein (144 vs 132 and 119 mg/dl,  $p=0.07$  and  $<0.001$ ) at baseline when compared to GDO-CKD and NG-CKD, respectively. Left ventricular mass index (LVMI) ( $36.0$  vs  $31.7$   $g/m^2$ ,  $p<0.001$ ) and the odds of LVH (OR: 3.38, 95%CI 1.42,8.08) at baseline were greater in FSGS-

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Correspondence and reprint requests to: Christine B. Sethna, MD, EdM, Division of Nephrology, 269-01 76th Avenue, New Hyde Park, NY 11040, csethna@northwell.edu, Phone: 718-470-3423, Fax: 718-470-0887.

Author's Contributions

Research idea and study design: CS, KM; data acquisition: DN, SJ; data analysis/interpretation: CS, KM, DN, SJ, BW, SF, JS; statistical analysis: DN, SJ; supervision or mentorship: CS, KM. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Disclosures

None

CKD compared to NG-CKD. Adjusted longitudinal analysis showed that FSGS-CKD had a faster decline in LVMI than NGCKD and FSGS-CKD had a faster increase in uric acid compared to both groups.

**Conclusions:** Children with CKD due to FSGS had a relatively high prevalence of CVD risk factors. FSGS was associated with greater CVD risk when compared to other CKD diagnoses.

### Keywords

glomerular disease; pediatrics; carotid intima medial thickness; left ventricular hypertrophy; hypertension; dyslipidemia

## Introduction

Focal segmental glomerulosclerosis (FSGS), the second leading cause of nephrotic syndrome in children, has increased in incidence in recent years and accounts for 11.7% percent of pediatric transplants in North America [1–3]. Beyond the risk of kidney morbidity, children with FSGS often have hypertension, prolonged exposure to medications and a pronounced alteration of lipoprotein metabolism that may place them at increased risk for adverse cardiovascular outcomes.

Hypertension is frequently a presenting feature of FSGS due to glomerular scarring and subsequent activation of the renin angiotensin aldosterone system, sodium/water retention and sympathetic nervous system activation [4]. In addition, medications used for FSGS treatment (e.g. steroids, calcineurin inhibitors) can cause hypertension. Unfortunately, some children do not achieve remission and continue to be nephrotic and/or hyperlipidemic. In addition to the risk of hyperlipidemia, genetic studies of lipoproteins have indicated that variants in *APOL1* increase both the risk for FSGS and atherosclerotic cardiovascular disease risk in African-American adults and children [5–7].

Recent studies from the Chronic Kidney Disease in Children (CKiD) cohort have shown that children with chronic kidney disease (CKD) often have increased arterial wall thickness, uncontrolled hypertension, masked hypertension, left ventricular hypertrophy (LVH) and dyslipidemia [8–11]. A population of children with FSGS is included in this cohort; however, little is known about the extent of cardiovascular disease (CVD) risk burden specifically in children with FSGS. Thus, the purpose of the current study was to characterize the cardiovascular health of children with FSGS enrolled in CKiD. In addition, we aimed to compare the CVD risk and longitudinal changes in CVD indicators among children with CKD secondary to FSGS with the CVD risk of children with CKD due to other glomerular disease and non-glomerular causes of CKD.

## Methods

### Study Design and Population

The CKiD study is a multi-center, prospective cohort of children with mild-moderate CKD. A total of 891 participants, aged 1–16 years with a diagnosis of CKD and an estimated glomerular filtration rate (eGFR)  $<90$  ml/min|1.73m<sup>2</sup> were enrolled at 54 sites in North

America from 2005–2014 in two recruitment waves [12]. Study visits consisted of data and biosample collection annually. Cardiovascular testing was performed every two years, starting with the year 2 visit, which included ambulatory blood pressure monitoring (ABPM), lipid studies, echocardiography and carotid intima medial thickness (cIMT, measured at selected sites). A full description of the CKiD study has been previously published [13]. The study protocol followed the Declaration of Helsinki and was approved by the Institutional Review Board at each participating site. Informed consent/assent was obtained from each participant.

Our study population was divided into three diagnosis categories for comparison: FSGS (FSGS-CKD), glomerular diagnosis other than FSGS (GDO-CKD) and nonglomerular disease (NG-CKD). Diagnoses were based on clinical chart review by CKiD site principal investigators. Primary versus secondary etiologies of FSGS were not recorded by CKiD. In addition, genetic data were not collected by CKiD, therefore, genetic vs. non-genetic forms of FSGS were not able to be distinguished in the cohort.

### Measures of Cardiovascular Health

Clinic blood pressure (BP) was measured using an aneroid sphygmomanometer (Mabis MedicKit 5, Mabis Healthcare, Waukegan, IL). The average of three readings was obtained from a sitting position after five minutes of rest. Systolic (SBP) and diastolic (DBP) BPs were transformed to BP z-scores and corresponding percentiles [14]. Hypertensive BP was defined as SBP or DBP  $\geq 95^{\text{th}}$  for age, sex and height or self-reported history of hypertension on anti-hypertensive medications. Uncontrolled hypertension was defined as hypertensive BP for those with a prior diagnosis of hypertension.

ABPM was measured and centrally read according to recommended guidelines (Spacelab 90217 monitors, Spacelabs Medical, Redmond, CA) [15]. Ambulatory hypertension was defined as clinic BP  $>95^{\text{th}}$  percentile, 24-hour SBP or DBP  $>95^{\text{th}}$  percentile and SBP or DBP load  $>25\%$  [16]. Masked hypertension was defined as clinic SBP and DBP  $<95^{\text{th}}$  percentile, 24-hour SBP or DBP  $>95^{\text{th}}$  percentile and SBP or DBP load  $>25\%$ . Children with mean systolic or diastolic nocturnal dip  $<10\%$  were classified as non-dippers [16, 17].

2D/M-mode echocardiography was performed for left ventricular (LV) measurements [18]. LV mass was calculated using the formula by Devereux et al [19]. LV mass index (LVMI) was derived by dividing LV mass (g) by the participant's height ( $\text{m}^{2.7}$ ) [20]. Values  $\geq 95^{\text{th}}$  percentile for age and sex indicated the presence of LVH [21]. Additionally, systolic and diastolic dysfunction was assessed by shortening fraction (SF), velocity of early (E-wave) and late (A-wave) diastolic trans-mitral flow, and E/A ratio.

B-mode ultrasonography cIMT was used to examine the common carotid arteries. The combined width of the intima plus the media was used as a measure of arterial wall thickness. Certified readings were obtained from the Cardiovascular Core Imaging Research Laboratory (Cincinnati, OH). cIMT z-scores were calculated for children  $\geq 6$  years old using normative reference data [22].

Fasting lipid studies (triglycerides, total cholesterol, high density lipoprotein [HDL] – cholesterol) were measured using a Bayer Advia 2400 analyzer. Non-HDL cholesterol was calculated as the difference between total cholesterol and HDL-cholesterol. Abnormally high triglycerides was defined as >110 mg/dl for children <10 years old, and >130 mg/dl for children ≥ 10 years old. Abnormal HDL and non-HDL cholesterol were defined as <40 mg/dl and >160 mg/dl, respectively [23]. Dyslipidemia was defined as the presence of any of these three abnormalities.

### Demographic, clinical and kidney health variables

Covariates of interest were age at diagnosis, age at study entry, race/ethnicity, maternal education, low birth weight (LBW, <2500g), and gestational age. Height, weight and body mass index (BMI) z-scores and percentiles were created [24]. BMI ≥ 85<sup>th</sup> percentile was categorized as overweight and BMI ≥ 95<sup>th</sup> percentile was categorized as obese. Blood chemistry included serum calcium (mg/dL), phosphorus (mg/dl) and uric acid (mg/dl). Renal health was assessed by eGFR (ml/min/1.73m<sup>2</sup>) using the 2012 Schwartz formula [12] and urine protein:creatinine ratio (UP/Cr) from the first morning urine. Nephrotic range proteinuria was defined as UP/Cr >2 mg/mg. Use of medications was self-reported.

### Statistical Analysis

For variables which were measured at every visit, baseline was defined as visit 1 (study entry), and for variables which were measured at only even visits, baseline was defined as visit 2 (1 year after study entry). Baseline characteristics of the three diagnosis groups were described and pairwise comparisons were based on the rank sum test and Fisher's exact test, as appropriate.

We fitted separate logistic regression models comparing CKD groups for outcomes of uncontrolled hypertension, LVH, dyslipidemia, and non-dipper status. Two models were fit for each outcome: the first was unadjusted, the second was adjusted for age, sex, race, overweight/obese status, cohort, and log transformed eGFR (to achieve normality) at the baseline visit.

To compare baseline and longitudinal changes of indicators of cardiovascular health, linear mixed effects models with random intercepts and slopes were used. Models were adjusted for baseline age, sex, race, overweight/obese status, recruitment wave, and log transformed eGFR at baseline. For LVMI, time-updated height was included instead of age since LVM is more strongly dependent on height [21]. Triglycerides, HDL-cholesterol and non-HDL cholesterol were log-transformed to achieve normality. Group-specific estimates and 95% confidence intervals (CI) for the initial level and slopes were derived from linear combinations of the model parameters. Pair-wise comparisons assessed how the GDO-CKD and NG-CKD groups were different from FSGS-CKD (as the reference group). Statistical significance was assessed at the p<0.05 level and all analyses were conducted in SAS 9.3 (SAS Institute, Carey, NC).

## Results

### Demographics and Therapy Use

A total of 891 children were enrolled in CKiD during the study period. Of these, 8.9% (79) were children with FSGS-CKD, 22.0% (196) had GDO-CKD and 69.1% (616) had NG-CKD. Table 1 presents participant characteristics at baseline. Those with FSGS-CKD tended to be of black race and with lower maternal education compared to non-FSGS groups. FSGS-CKD was more likely to be of LBW and premature compared to the GDOCKD group. The FSGS-CKD group was more likely to have a biological family member with FSGS compared to the other etiologic groups. When compared to NG-CKD, children with FSGS-CKD were older, less likely male and heavier. The median age of CKD onset was 9 years for those with FSGS-CKD and 7.5 years for GDO-CKD, compared to birth for those with NG-CKD. The median eGFR among children with FSGS was lower compared to GDO-CKD, and higher compared to children with NGCKD. The proportion with nephrotic range proteinuria was substantially higher among those with FSGS-CKD. Children with FSGS-CKD and GDO-CKD had similar proportions receiving antihypertensive therapy, corticosteroids and any immunosuppressive therapy. The prevalence of these therapies was higher among these two groups compared to those with NG-CKD. The use of diuretic and lipid lowering medication was higher in the FSGS-CKD group than in the other two groups.

### Cardiovascular Risk Profile for FSGS

Table 2 presents the characteristics at baseline for cardiovascular variables. A substantial proportion of children with FSGS-CKD had abnormal BP parameters including 24.4% with uncontrolled clinic BP, 24.6% with confirmed ABPM hypertension, and 46.2% with masked HTN. Nocturnal non-dipper status was present in 51%. LVH was present in 26.3% of FSGS-CKD with eccentric hypertrophy in 17.5% and concentric hypertrophy in 8.8%. The prevalence of dyslipidemia was 60.0% in those with FSGS-CKD, with 29.3% having 2 lipid abnormalities. The median cIMT z-score was 0.68 (IQR -0.21, 1.57) (excluding 50 observations from children <6 years due to lack of normative reference data) [22].

### Comparison of Cardiovascular Risk among CKD Groups

At baseline, there were significant differences in cardiovascular markers between FSGS-CKD and non-FSGS CKD groups. Children with FSGS-CKD had significantly higher median SBP z-score, uric acid and triglycerides, as well as a greater prevalence with LVH, high non-HDL cholesterol and dyslipidemia compared to the other CKD groups (Table 2). Children with FSGS-CKD also had higher ambulatory BP and LVMI compared to children with GDO-CKD. Children with FSGS-CKD had more diastolic non-dipping and abnormal LV geometry, but lower Ca × P product values compared to children with NG-CKD. No significant differences in E/A ratio or cIMT values were found among the groups.

Table 3 shows the association between cardiovascular outcomes and CKD diagnosis. In unadjusted analyses, FSGS-CKD was a risk factor for all cardiovascular outcomes examined (i.e., the odds ratios > 1), however, only LVH, dyslipidemia and diastolic dipping were significant. In models adjusting for age, gender, race, BMI category, cohort wave and eGFR, restricting to those with NG-CKD and FSGS-CKD, only LVH and dyslipidemia were

significantly associated with FSGS. It should be noted that the overall odds ratio estimates for each outcome remained  $> 1$  (i.e., increased risk), but those with FSGS were not significantly different than GDO-CKD.

### Longitudinal Changes

Figure 1 shows the adjusted estimates of baseline levels and longitudinal changes in cardiovascular markers across the diagnosis groups. The number of visits per participant for each cardiovascular variable is presented in Supplementary Table 1. FSGS-CKD had higher SBP z-scores at baseline than in the other two groups, but the change over time was not significantly different across diagnosis groups. DBP z-scores were not significantly different at baseline and change over time was not different by CKD group. LVMI was higher among those with FSGS-CKD compared to those with NG-CKD. LVMI decreased over time among all the three groups, and children with FSGS had a faster decline in LVMI than children with NG-CKD. No significant differences in either baseline values or changes over time were detected for cIMT. We also investigated age- and gender-specific cIMT z-scores based on previously published reference values and found no evidence of differences across diagnostic groups (data not shown). Those with FSGS-CKD had increasing uric acid over time and this was a significantly faster increase compared to those with GDO-CKD and NG-CKD. Children with FSGS-CKD had a higher concentration of non-HDL cholesterol and triglycerides at baseline than children with the other two CKD diagnoses. For FSGS-CKD, average triglycerides decreased 0.50% per year, which was borderline significantly ( $p = 0.05$ ) different from the NGCKD group, who had a faster increase of 3.71% per year. There were no significant differences in baseline HDL among the three groups. Those with FSGS-CKD entered the study with a lower eGFR and had a significantly faster decline than the other etiologic groups. The average change was  $-12.5\%$  per year for those with FSGS-CKD; those with GDO-CKD declined nearly 10% per year, while those with NG-CKD declined approximately 7% per year.

### Discussion

This analysis of a multi-center, national cohort of children with mild-moderate CKD demonstrated that the CVD risk factors of ambulatory hypertension, masked hypertension, non-dipper status, LVH and dyslipidemia are prevalent in children with FSGS. Additionally, we found that FSGS was associated with a worse cardiovascular risk profile when compared with other CKD diagnoses. Children with FSGS had greater SBP z-scores and triglycerides at baseline compared to non-FSGS CKD. Non-HDL cholesterol, LVMI and LVH at baseline were also greater in children with FSGS than in the NG-CKD cohort. Longitudinal analysis showed children with FSGS had a faster decline in LVMI compared to NG-CKD and FSGS had a faster increase in uric acid compared to both CKD groups.

FSGS, the most common primary glomerular disorder in children causing ESRD, is a complex disease that remains only partially understood [2]. Our finding that the FSGS cohort had increased cardiovascular risk compared to non-FSGS CKD is likely multifactorial, being related to the severity of ongoing proteinuria and exposure to multiple immunosuppressive medications with cardiovascular side-effects. In addition, genetic

variants in *APOL1* have been shown to confer increased risk of both FSGS and CVD in African-American adults and children [5–7]. Furthermore, obesity, lower socioeconomic status with reduced opportunity to exercise and decreased access to healthy food, altered Vitamin D metabolism, and disease specific related factors may contribute to the cardiovascular risk in this population [23, 25–27].

Children with FSGS have a more rapid onset of CKD at an older age with subsequent greater exposure to immune modulating agents which are likely to have an increased effect on obesity and the progression of disease than in non-FSGS cohorts, especially when compared to non-glomerular CKD. In this study, children with NGCKD whose renal disorders were commonly due to congenital abnormalities, had a longer time since disease onset and a lower eGFR compared to FSGS-CKD, and yet FSGS-CKD had a worse cardiovascular profile, suggesting that FSGS is associated with a more aggressive cardiovascular burden. Interestingly, the FSGS-CKD cardiovascular profile was also worse when compared to GDO-CKD, even though disease duration, age of onset, weight status and medication exposure were similar in the latter cohort.

As mentioned previously, children with FSGS are at risk for hypertension for a variety of reasons [28]. Despite the fact that 94% of children with FSGS in our study were on anti-hypertensive medication, 25% had ambulatory hypertension, 46% had masked hypertension and their clinical SBP z-score did not change over time, further documenting that hypertension is not adequately being treated in this population. Previous studies that describe the high burden of hypertension and its suboptimal control among children with FSGS are consistent with these results [29, 30].

The literature on LVH and other target organ effects in children with FSGS is limited. A small single center study reported LVH in 56% (10/18) of nephrotic children with a podocin mutation, a mutation known to cause FSGS [31]. In another CKiD study, Woroniecki et al. found that African-American children with FSGS and the high risk *APOL1* genotype had increased odds of LVH and obesity compared to children with the *APOL1* low risk genotype [6]. There is mounting evidence that obesity is relevant to CVD as demonstrated by the strong association between obesity and LVH in children in the general population, which is independent of BP [32]. Hemodynamic, metabolic and inflammatory factors are thought to contribute to the development of LVH in obese children [33]. In this study, however, although the children with FSGS were significantly more obese than those with NG-CKD, obesity alone was likely not responsible for differences in LVMI and LVH as children with FSGS still had greater LVMI and LVH compared to NG-CKD children after adjusting for weight status.

Given that lipoprotein metabolism is known to be altered in nephrotic syndrome, the finding of greater dyslipidemia in FSGS children compared to the non-FSGS cohort was not unexpected. In nephrotic syndrome, lipid abnormalities typically include elevated total cholesterol, LDL, VLDL, triglycerides and apolipoprotein B with varied HDL levels [34]. These lipid changes are due to decreased lipoprotein lipase activity in the liver and peripheral tissues, increased biosynthesis in the liver, and compositional changes of the lipoproteins [34]. However, the role of hyperlipidemia on the long-term risk of

atherosclerosis and CVD in children with FSGS is not fully understood. There were no differences in cIMT, a surrogate for atherosclerosis, between FSGS and non-FSGS children in our study, which may be explained in part by the small sample size that completed cIMT testing in the FSGS group. A study by Brady et al. demonstrated that cIMT in children in CKiD was elevated compared with healthy children [35].

These findings in children with FSGS highlight a critical need to improve identification and treatment of these CVD comorbidities in this high-risk population. Clinicians should focus on rigorous BP control in children with FSGS [36] and greater attention should be paid to metabolic factors including lipid management [23, 34]. These children also require dietary interventions and support to improve nutrition and to control weight while maximizing the opportunity for exercise [23]. The protracted use of glucocorticoids also requires careful evaluation in each case.

Although this study has several strengths, including longitudinal follow-up and the standardization of testing measures, there are limitations that should be considered. The sample size of the FSGS group was relatively small compared to the rest of the cohort and thus the study may not be powered to be generalizable to the pediatric FSGS population. In addition, FSGS is a histologic lesion with heterogeneous etiologies; genetic data and information on primary vs. secondary causes of FSGS was lacking. Another potential limitation was the comparison of FSGS with two diagnostic categories that have markedly different pathologies and disease courses, particularly the congenital renal abnormalities. Indeed, the burden of years with CKD was much longer for those with congenital diagnoses compared to those with FSGS. Lastly, given the lack of data about the duration and cumulative dose of immunosuppressive/steroid therapy, we are unable to discern whether the excess in CVD risk factors is due to diagnosis alone or the cumulative burden of these therapies.

## Conclusion

Our study provides evidence that children with FSGS are at significantly increased CVD risk due to a combination of medication exposure, poorly controlled hypertension over time, masked hypertension, LVH and dyslipidemia. Of importance, children with FSGS and mild-moderate CKD have greater CVD risk when compared to other CKD related diagnoses. Our findings strongly support the notion that children with FSGS should undergo screening for CVD risk factors and that these should be monitored on a regular basis. Treatment needs to be aimed at minimizing the impact that these risk factors have on the children's cardiovascular well-being. Future longitudinal studies with longer term follow-up (i.e. > 5 or 10 years) are needed to determine what interventions best reduce adverse cardiovascular outcomes for children with FSGS.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.



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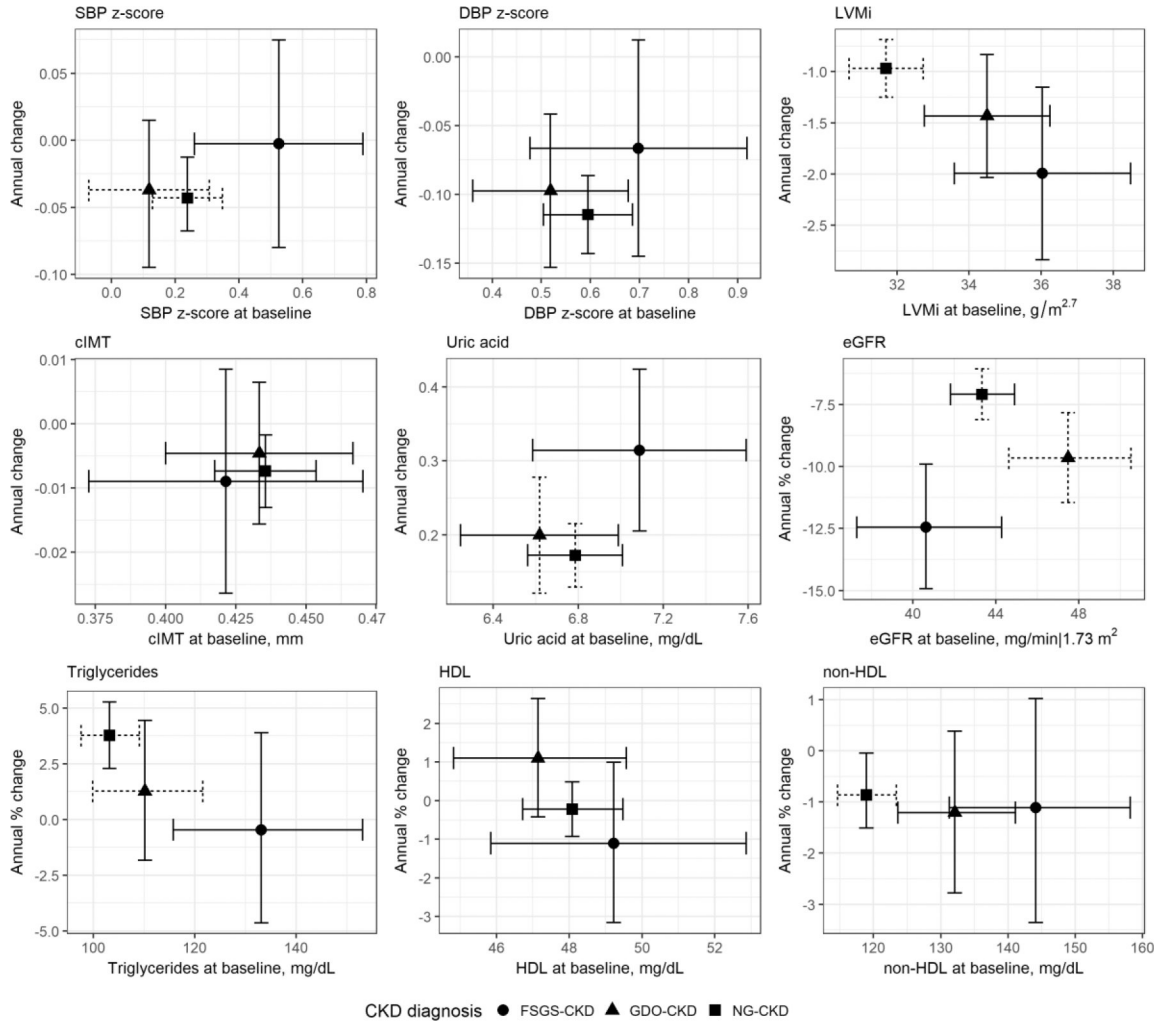
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**Figure 1.** Longitudinal changes in cardiovascular indicators based adjusted<sup>3</sup> linear mixed effects models with random intercepts and random slopes comparing CKD diagnosis groups. Dashed horizontal bar: Intercept statistically different ( $p < 0.05$ ) from FSGS-CKD group. Dashed vertical bar: Slope (or annual % change) statistically different from FSGS-CKD group. Models were adjusted for age (all outcomes except for LVMi), sex, race, overweight/obese status, cohort wave and eGFR (log transformed). For interpretation of intercept, the reference characteristic was for a non-black, 10 year old normal weight boy from cohort wave 1 whose eGFR at baseline was 45 ml/min|1.73m<sup>2</sup>; for LVMi model: time-updated height (centered at 150 cm) was included instead of age as a covariate. CKD - chronic kidney disease; FSGS - focal segmental glomerulosclerosis; G - glomerular; NG - non-glomerular; SBP - systolic blood pressure; DBP - diastolic blood pressure; BMI - body mass index;

**Table 1.**

Baseline demographic, growth, chronic kidney disease and therapy characteristics of participants in the Chronic Kidney Disease in Children (CKiD) cohort, by underlying CKD diagnosis.

Variable	FSGS-CKD N = 79	GDO-CKD N = 196	NG-CKD N = 616	P value comparing FSGS-CKD to GDO-CKD	P value comparing FSGS-CKD to NG-CKD
<b>Demographic and birth history</b>					
Age at study entry, years	14.5 [10.3, 15.8]	13.9 [10.8, 15.9]	10.1 [6.5, 13.6]	0.82	<0.001
Male sex	54.4% (43)	53.1% (104)	65.7% (405)	0.84	<b>0.048</b>
Black race	54.4% (43)	20.9% (41)	18.7% (115)	<0.001	<0.001
Maternal education college level or higher	44.2% (34)	59.8% (113)	62.3% (376)	<b>0.02</b>	<b>0.002</b>
Low birth weight (< 2500g)	23.6% (17)	12.2% (22)	19.6% (115)	<b>0.02</b>	0.42
Premature birth (< 36 weeks)	15.5% (11)	6.8% (13)	12.6% (75)	<b>0.03</b>	0.49
CKiD II recruitment	45.6% (36)	56.6% (111)	25.6% (158)	0.09	<0.001
Duration of follow up (years)	3.0 [1.1, 4.4]	2.9 [1.8, 4.0]	4.3 [3.0, 7.0]	0.88	<0.001
Any relative with FSGS	9.7% (7)	1.1% (2)	0.7% (4)	<0.001	<0.001
<b>Growth</b>					
Height z-score	-0.28 [-1.31, 0.24]	-0.18 [-0.94, 0.70]	-0.61 [-1.45, 0.16]	0.06	0.21
Weight z-score	0.56 [-0.32, 1.98]	0.64 [-0.23, 1.57]	-0.13 [-0.97, 0.74]	0.99	<0.001
BMI z-score	0.92 [0.16, 2.01]	0.93 [-0.02, 1.60]	0.32 [-0.43, 1.21]	0.35	<0.001
BMI categories				0.50	<0.001
Normal (< 85 <sup>th</sup> percentile)	51.9% (41)	55.9% (109)	70.7% (419)		
Overweight (85 <sup>th</sup> to < 95 <sup>th</sup> percentile)	17.7% (14)	20.5% (40)	14.7% (87)		
Obese (> 95 <sup>th</sup> percentile)	30.4% (24)	23.6% (46)	14.7% (87)		
<b>Chronic Kidney Disease</b>					
Age at CKD onset, years	9.0 [4.5, 12.5]	7.5 [2.5, 12.5]	0.0 [0.0, 0.0]	0.3	<0.001
Proportion of life with CKD	32.5 [15.5, 61.5]	29.5 [9.7, 68.9]	100.0 [100.0, 100.0]	0.89	<0.001
eGFR (ml/min/1.73m <sup>2</sup> )	56.0 [39.0, 67.2]	62.5 [45.2, 78.5]	49.4 [36.7, 61.9]	<b>0.02</b>	<b>0.03</b>
Urine protein:creatinine, mg/mg	1.11 [0.30, 4.17]	0.61 [0.19, 1.80]	0.28 [0.11, 0.80]	<b>0.02</b>	<0.001
Nephrotic proteinuria (>2.0 mg/mg)	32.0% (24)	22.0% (42)	8.3% (49)	0.089	<0.001
<b>Therapy use</b>					
Any anti-hypertensive medication	93.7% (74)	90.8% (178)	53.4% (329)	0.44	<0.001
ACE inhibitor	75.9% (60)	70.9% (139)	39.9% (246)	0.4	<0.001
ARB	31.6% (25)	21.9% (43)	6.0% (37)	0.09	<0.001
Diuretic	20.3% (16)	10.2% (20)	4.2% (26)	<b>0.025</b>	<0.001
Corticosteroid	24.1% (19)	32.7% (64)	1.1% (7)	0.16	<0.001
Any immunosuppressive medication	51.9% (41)	42.9% (84)	1.3% (8)	0.17	<0.001
Lipid lowering medication	24.1% (19)	4.1% (8)	1.0% (6)	<0.001	<0.001

CKD - chronic kidney disease; FSGS-CKD - focal segmental glomerulosclerosis group; GDO-CKD - glomerular disease other group; NG-CKD - non-glomerular group; eGFR - estimated glomerular filtration rate; BMI - body mass index; ACE - angiotensin converting enzyme; ARB - angiotensin II receptor blocker

**Table 2.**

Baseline characteristics of cardiovascular health indicators among participants, by underlying CKD diagnosis.

Variable	FSGS-CKD N = 79	GDO-CKD N = 196	NG-CKD N = 616	P value comparing FSGS-CKD to GDO-CKD	P value comparing FSGS-CKD to NG-CKD
<b>Blood Pressure</b>					
SBP z-score	0.60 [-0.02, 1.38]	0.03 [-0.76, 0.97]	0.42 [-0.30, 1.11]	<b>&lt;0.001</b>	<b>0.04</b>
DBP z-score	0.47 [-0.10, 1.17]	0.22 [-0.42, 0.86]	0.56 [-0.04, 1.18]	0.05	0.58
Measured BP status				0.163	0.639
Normal (<90 <sup>th</sup> percentile)	66.2% (51)	76.2% (147)	68.4% (405)		
Prehypertension (90 <sup>th</sup> to < 95 <sup>th</sup> percentile)	9.1% (7)	8.8% (17)	11.1% (66)		
Hypertension (> 95 <sup>th</sup> percentile)	24.7% (19)	15.0% (29)	20.4% (121)		
Uncontrolled hypertensive clinic BP	24.4% (19)	14.9% (29)	19.9% (121)	0.06	0.36
Ambulatory and clinic BP categories				<b>0.01</b>	0.17
White coat hypertension	3.1% (2)	1.8% (3)	2.1% (11)		
Masked hypertension	46.2% (30)	55.8% (91)	54.0% (285)		
Confirmed hypertension	24.6% (16)	8.6% (14)	14.4% (76)		
SBP dipping < 10%	47.1% (24)	38.3% (49)	39.5% (175)	0.28	0.3
DBP dipping < 10%	31.4% (16)	18.8% (24)	15.6% (69)	0.07	<b>0.005</b>
Non dipper status	51.0% (26)	39.8% (51)	40.4% (179)	0.17	0.15
<b>Cardiovascular Tests</b>					
Left ventricular mass index, g/m <sup>2.7</sup>	31.4 [27.4, 39.6]	28.7 [24.9, 34.8]	31.5 [25.6, 37.6]	<b>0.02</b>	0.27
LVH	26.3% (15)	11.0% (16)	10.9% (52)	<b>0.007</b>	<b>&lt;0.001</b>
Left ventricular geometry				0.06	<b>0.007</b>
Normal	68.4% (39)	80.7% (117)	78.9% (378)		
Eccentric Hypertrophy	17.5% (10)	7.6% (11)	6.5% (31)		
Concentric Remodeling	5.3% (3)	8.3% (12)	10.2% (49)		
Concentric Hypertrophy	8.8% (5)	3.4% (5)	4.4% (21)		
Shortening Fraction	0.37 [0.34, 0.41]	0.36 [0.33, 0.39]	0.38 [0.34, 0.42]	0.15	0.27
E/A ratio	1.7 [1.6, 2.3]	1.9 [1.5, 2.3]	1.8 [1.5, 2.3]	0.81	0.68
Carotid Artery Intima-Medial Thickness, mm	0.43 [0.32, 0.47]	0.41 [0.35, 0.46]	0.42 [0.37, 0.48]	0.85	0.67
<b>Biomarkers</b>					
Uric acid, mg/dL	6.5 [5.7, 7.3]	5.8 [4.8, 6.8]	5.8 [4.7, 7.0]	<b>0.005</b>	<b>0.005</b>
Calcium, mg/dL	9.4 [8.9, 9.7]	9.3 [8.8, 9.6]	9.6 [9.3, 9.9]	0.84	<b>&lt;0.001</b>
Phosphorus, mg/dL	4.4 [3.8, 4.9]	4.4 [3.7, 4.8]	4.5 [4.1, 5.0]	0.83	0.13
Ca × P product	40.0 [35.5, 45.5]	39.8 [35.1, 45.1]	43.2 [38.8, 47.5]	0.95	<b>&lt;0.001</b>
<b>Lipid levels</b>					
Diabetes Mellitus at baseline	0.0% (0)	3.6% (7)	0.3% (2)	0.2	1.00
Ever diagnosed with Diabetes Mellitus during study follow-up	3.8% (3)	6.2% (12)	2.1% (13)	0.57	0.41
Triglycerides, mg/dL	121 [86, 191]	93 [70, 149]	97 [72, 140]	<b>0.01</b>	<b>0.01</b>

Variable	FSGS-CKD N = 79	GDO-CKD N = 196	NG-CKD N = 616	P value comparing FSGS-CKD to GDO-CKD	P value comparing FSGS-CKD to NG-CKD
High triglycerides	49.2% (32)	31.5% (53)	42.4% (231)	<b>0.01</b>	0.29
HDL cholesterol, mg/dL	53 [41, 61]	50 [40, 60]	49 [42, 58]	0.38	0.24
Low HDL cholesterol	6.2% (4)	9.5% (16)	9.0% (49)	0.41	0.44
Non-HDL cholesterol, mg/dL	121 [108, 162]	118 [95, 145]	118 [97, 138]	0.06	<b>0.02</b>
High non-HDL cholesterol	27.7% (18)	14.9% (25)	10.3% (56)	<b>0.02</b>	<b>&lt;0.001</b>
Counts of abnormal lipids values (out of 3)				0.07	<b>0.02</b>
0	40.0% (26)	58.9% (99)	56.8% (310)		
1	30.8% (20)	22.6% (38)	26.0% (142)		
2	23.1% (15)	14.3% (24)	15.2% (83)		
3	6.2% (4)	4.2% (7)	2.0% (11)		
Dyslipidemia	60.0% (39)	41.1% (69)	43.2% (236)	<b>0.009</b>	<b>0.01</b>

CKD - chronic kidney disease; FSGS-CKD - focal segmental glomerulosclerosis group; GDO-CKD - glomerular disease other group; NG-CKD - non-glomerular group; SBP - systolic blood pressure; DBP - diastolic blood pressure; BP - blood pressure; LVH - left ventricular hypertrophy; E - early wave diastolic trans-mitral flow; A - late wave diastolic trans-mitral flow; Ca x P calcium x phosphorus; HDL - high density lipoprotein.

**Table 3.**

Association between cardiovascular and metabolic outcomes and CKD diagnosis at analytical baseline

Outcome	Comparison	Unadjusted	Adjusted <sup>a</sup>
Uncontrolled hypertension	FSGS-CKD vs. GDO-CKD	1.84 (0.96, 3.53)	1.30 (0.60, 2.83)
	FSGS-CKD vs. NG-CKD	1.30 (0.74, 2.26)	1.63 (0.87, 3.05)
Left ventricular hypertrophy	FSGS-CKD vs. GDO-CKD	<b>2.88 (1.31, 6.32)</b>	1.30 (0.49, 3.47)
	FSGS-CKD vs. NG-CKD	<b>2.93 (1.52, 5.65)</b>	<b>3.38 (1.42, 8.08)</b>
Dyslipidemia	FSGS-CKD vs. GDO-CKD	<b>2.15 (1.20, 3.86)</b>	1.75 (0.87, 3.50)
	FSGS-CKD vs. NG-CKD	<b>1.96 (1.16, 3.32)</b>	<b>2.31 (1.21, 4.44)</b>
Diastolic dipping < 10%	FSGS-CKD vs. GDO-CKD	1.98 (0.95, 4.15)	1.46 (0.62, 3.43)
	FSGS-CKD vs. NG-CKD	<b>2.48 (1.30, 4.72)</b>	1.96 (0.92, 4.18)
Systolic dipping < 10%	FSGS-CKD vs. GDO-CKD	1.43 (0.74, 2.76)	1.30 (0.63, 2.69)
	FSGS-CKD vs. NG-CKD	1.36 (0.76, 2.44)	1.13 (0.59, 2.18)
Non dipper status	FSGS-CKD vs. GDO-CKD	1.57 (0.82, 3.02)	1.36 (0.66, 2.80)
	FSGS-CKD vs. NG-CKD	1.53 (0.86, 2.74)	1.30 (0.68, 2.50)

<sup>a</sup>Adjusted for age, gender, race, overweight/obese status, cohort wave and eGFR (log transformed)