Cardiometabolic Risk Factors, Metabolic Syndrome, and Chronic Kidney Disease Progression in Children

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Objective To estimate the prevalence of metabolic syndrome (MetS) and examine its association with chronic kidney disease progression in children enrolled in the Chronic Kidney Disease in Children study.

Study design MetS was defined as being overweight or obese and having ≥2 cardiometabolic risk factors (CMRFs). Incidence and prevalence of MetS were assessed using pairs of visits approximately 2 years apart.

Results A total of 799 pairs of person-visits (contributed by 472 children) were included in the final analysis. Of these, 70% had a normal body mass index (BMI), 14% were overweight, and 16% were obese. At the first visit, the prevalence of MetS in the overweight group was 40% and in the obese group was 60%. In adjusted models, annual percent estimated glomerular filtration rate decline in those who had normal BMI and incident or persistent multiple CMRFs or those with persistent MetS was −6.33%, −6.46%, and −6.08% (respectively) compared with children who never had multiple CMRFs (−3.38%, \( P = .048 \), .045, and .036, respectively). Children with normal BMI and incident multiple CMRFs and those with persistent MetS had approximately twice the odds of fast estimated glomerular filtration rate decline (>10% per year) compared with those without multiple CMRFs and normal BMI.

Conclusion Children with chronic kidney disease have a high prevalence of MetS. These children as well as those with normal BMI but multiple CMRFs experience a faster decline in kidney function. (J Pediatr 2018;123:163–172).

Cardiovascular and metabolic health are important in the management of pediatric chronic kidney disease (CKD). Children with CKD have excess cardiovascular risk factors, and many suffer from metabolic conditions such as obesity.1 The interaction between cardiovascular and metabolic health in the context of CKD presents a challenge in terms of stratifying risk. The clustering of cardiometabolic risk factors (CMRFs) such as insulin resistance, dyslipidemia, hypertension, and obesity is termed metabolic syndrome (MetS). The presence of MetS is associated with a greater incidence of CKD and, among adult patients with established CKD, with a more rapid decline in glomerular filtration rate (GFR).2,3 MetS is relatively uncommon in children. A recent systemic review estimated the median prevalence to be 3.3% (range 0%-19.2%).4 We previously demonstrated that nearly 40% of pediatric patients undergoing kidney transplant met criteria for MetS at 1 year after renal transplantation, and a substantial percentage (28%) of these patients had developed MetS during the first posttransplant year, mostly due to an increased prevalence of obesity and associated cardiovascular risk factors.5 Although the prevalence of obesity in children with CKD before kidney transplant is similar to that in the general population, patients with CKD have a greater prevalence of other traditional cardiovascular risk factors. For example, almost one-half of the children enrolled in the Chronic Kidney Disease in Children (CKiD) multicenter observational study of children with CKD stage 2-4 had hypertension and dyslipidemia, and about one-third of them had a combination of at least 2 CMRFs.3 These data suggest that as in kidney transplant recipients, MetS is likely more frequent in children with CKD than in the general population of children.

The goal of this study was to estimate the prevalence and incidence of MetS in children with mild-to-moderate CKD and to examine its association with CKD progression.

BMI Body mass index
CKD Chronic kidney disease
CKiD Chronic Kidney Disease in Children
CMRF Cardiometabolic risk factor
eGFR Estimated glomerular filtration rate
GFR Glomerular filtration rate
MetS Metabolic syndrome

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progression in children enrolled in the CKiD study. We hypothesized that a significant proportion of children will meet criteria for the diagnosis of MetS and that the presence of MetS will be associated with a more rapid decline in kidney function.

Methods

CKiD is a multicenter, observational prospective cohort study of the natural history and progression of pediatric CKD. A total of 891 children have been enrolled, ages between 1 and 16 years and an estimated glomerular filtration rate (eGFR) 30-90 mL/min/1.73 m⁴ at 54 clinical sites in the US and Canada. Full details of the study design, structure, and research procedures have been published previously. To summarize, during the annual CKID study visit, each subject had height, weight, and manual blood pressure measured. The laboratory data included a basal metabolic profile, cystatin C, urine protein to creatinine ratio, lipid profile, and fasting blood glucose. The study design and protocols were approved by institutional review boards at each site and by an external study monitoring board appointed by the National Institute of Diabetes and Digestive and Kidney diseases.

Metabolic Syndrome

MetS was defined as the presence of overweight or obesity as defined by an age- and sex-specific body mass index (BMI) >85th percentile, as well as having 2 or more CMRFs (high triglycerides; low HDL cholesterol, hypertension, and impaired fasting plasma glucose levels). Abnormally high triglycerides were defined as being greater than or equal to the age- and sex-specific 95th percentiles, and abnormally low HDL was defined as being less than or equal to the age- and sex-specific 5th percentile. Elevated systolic or diastolic blood pressure or hypertension was defined as being greater than or equal to the age- and sex-specific 90th percentile or self-reported hypertension with use of antihypertensive therapies. Impaired fasting plasma glucose was defined as being >100 mg/dL. Triglycerides and cholesterol were measured at the second annual CKID study visit and every 2 years thereafter. On the basis of the BMI, the MetS phenotypes were categorized as mild MetS phenotype (BMI 85-95th percentile and ≥2 CMRFs) and severe MetS phenotype (BMI ≥95th percentile and ≥2 CMRFs). In addition to categorizing MetS as the presence of high BMI with at least 2 CMRFs, we also categorized the presence of multiple CMRFs among children who had a normal BMI (ie, age and sex-specific BMI between 5th and 85th percentiles). This allowed us to evaluate the 2 distinct groups in addition to those with elevated BMI and MetS: the “metabolically healthy overweight or obese” ie, high BMI without ≥2 CMRFs and the “metabolically unhealthy normal BMI,” ie, normal BMI with ≥2 CMRFs.

To characterize different patterns of multiple CMRFs and MetS, we used pairs of person-visits (approximately 2 years apart) as the unit of observation. Specifically, if a participant contributed 3 visits, 2 pairs of consecutive person-visits were obtained. BMI categories (normal, overweight, or obese) for pairs of visits were restricted to the index (or first) visit of each pair as the children’s BMI z scores were stable from the index visit to the follow-up visit (Pearson correlation coefficient = 0.89). Among children who had an elevated BMI at their first visit, the classifications of MetS were defined as never MetS (in which the index and subsequent visits were free of multiple CMRFs), incident MetS (in which the index visit, but not the subsequent visit, was free of multiple CMRFs), resolved MetS (in which the index visit had multiple CMRFs, but the subsequent visit did not), and persistent MetS (in which both visits had multiple CMRFs). Similar categories were constructed for those with normal BMI at index visit but were denoted as multiple CMRFs.

Outcomes

In addition to describing the prevalence and incidence of MetS and multiple CMRFs, we also characterized change in eGFR in our sample of person-visits. Estimated GFR was measured at each annual visit and based on the full 2012 CKiD equation using data on serum creatinine, cystatin c, and blood urea nitrogen. Annual change in kidney function was calculated as the difference in eGFR in the log scale between the index visit (i) and the follow-up visit (i +1) divided by the difference in time (in years) between the 2 visits:

$$\text{annual change in log(eGFR)} = \frac{\log(eGFR_{i+1}) - \log(eGFR_i)}{t_{i+1} - t_i}$$

The annual percent change in eGFR was calculated as $\exp(\text{annual change in log(eGFR)} - 1) \times 100\%$. In addition to describing the annual percent change in eGFR as a continuous variable, we dichotomized this variable to define fast progression as an annual decline in eGFR greater than 10%.

Statistical Analyses

The analytic approach comprised 3 main comparisons. First, the distributions of demographic and clinical characteristics, as well as prevalence of each CMRF, were compared by BMI categories at the index visit to describe differences by BMI. Pairwise comparisons with normal BMI as the reference group were calculated with the Wilcoxon rank sum test for continuous characteristics and were calculated with the $\chi^2$ test for categorical (including binary) characteristics. Second, distributions of demographic and clinical characteristics were compared within each BMI category by the presence of at least 2 CMRFs to describe associations related to multiple CMRFs, using the same methods as described previously. Lastly, we formally compared children who had multiple CMRFs (among children with normal BMI at index visit) or MetS at either visit (pooling individuals who were overweight or obese at the index visit) with those with normal BMI at the index visit and who did not have multiple CMRFs at either visit, which resulted in
in a total of 8 groups (1 reference group and 7 comparison groups). For formal statistical comparisons, linear regression models were fit with annual difference in log(eGFR) as the dependent variable and group membership as categorical independent variables (with normal BMI and never multiple CMRFs as the reference group). Logistic regression models were fit with the dependent variable being fast progression (ie, percent decline in GFR >10% per year). Univariate (ie, unadjusted) models were reported as well as models adjusted for CKD diagnosis (glomerular vs nonglomerular; Pierce et al\textsuperscript{11}), sex, self-reported African-American race, CKD duration (in years), corticosteroid use, and maternal college education as a proxy for socioeconomic status. These covariates were expected to be associated with high BMI and metabolic abnormalities and accelerated disease progression. Adjustments for these variables were incorporated using inverse probability of exposure weights. Generalized estimation equations was used to account for within-subject correlations. Statistical significance was assessed at the $P < .05$ level. All statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, North Carolina) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

Of the 891 participants, a total of 472 contributed 799 pairs of person-visits with complete data. Figure 1 displays the inclusion of the participants and their corresponding pairs of person-visits. Those included in the final analysis had a BMI >5th percentile and complete data for CMRFs, eGFR, and covariates. Among these, 560 (70%) had a normal BMI, 112 (14%) were overweight, and 127 (16%) were obese at the index visit.

![Diagram](image-url)  
**Figure 1.** Description of the selection of participants and pairs of visits that contributed to the analytic study population. *Covariates: CKD diagnosis, maternal education, sex, race, CKD duration (in years), and corticosteroid use.
Table I presents the characteristics at the index visit by BMI categories among 799 pairs of person-visits. The median age and proportion of boys among different BMI groups were similar. The proportion of household income <$36,000 was approximately 40% across the 3 groups, but lower level of maternal education was observed in the obese group as compared with the normal BMI group (P = .07).

The prevalence of glomerular CKD diagnoses was greater with increasing BMI: 12% among those with normal BMI, 21% among overweight, and 28% among obese. The time since CKD onset at the index visit was approximately 10 years for children across the 3 BMI groups. The eGFR was significantly lower and urine protein creatinine ratio was significantly greater in the overweight group, and 28% among obese. The time since CKD onset at the index visit was approximately 10 years for children across the 3 BMI groups. The eGFR was significantly lower and urine protein creatinine ratio was significantly greater in the overweight group, and 28% among obese.

Among CMRFs, the prevalence of high triglycerides and low HDL cholesterol were significantly greater in the overweight and obese groups (Table I). Hypertension was greater only in the obese group. The distributions of cumulative CMRFs (ie, the cumulative frequencies of these 4 CMRFs) differed between the normal BMI and obese groups. Although the overweight group had a greater burden of cumulative CMRFs compared with the normal BMI group, this difference was not significant.

Table II presents the characteristics at index visit by number of CMRFs, stratified by BMI categories. For those with a normal BMI, 29% had at least 2 CMRFs. In contrast, the prevalence of multiple CMRFs was 51% in the overweight/obese participants: 40% in the overweight group and 60% in the obese group (these 2 groups are defined as having MetS). Regardless of BMI category at the index visit, children with ≥2 CMRFs were similar to children with none or one CMRF in terms of age, CKD duration, race, and maternal education. Among overweight children, those with MetS had a greater prevalence of lower household income (ie, <$36,000; P = .002). Within each BMI category, eGFR was significantly lower and urine protein creatinine ratio was significantly greater in the ≥2 CMRFs group compared with the <2 CMRFs group.

Figure 2 displays the annual percent changes in eGFR from index visit to follow-up visit with corresponding changes in MetS or multiple CMRFs classifications, stratified by BMI status at the index visit. Among participants with a normal BMI who never had multiple CMRFs, the median percent change in eGFR was −2.4% per year. In this group, the proportion of those who declined at least 10% per year (ie, fast decline) was 15.9%. Participants with persistent multiple CMRFs, regardless of BMI category (normal or MetS), had a consistently faster decline (25%-29%) than those who had no multiple CMRFs at any time. Within each BMI category, there were similar distributions of change between incident and resolved multiple CMRFs/MetS, although there were few people contributing to these classifications in the overweight and obese categories. Indeed, those who had MetS were most likely to have persistent MetS between the 2 visits. Within each BMI category, the median percent eGFR change was most substantial among those with
multiple CMRFs ranging from $-4.52\%$ per year (normal BMI group) to $-6.65\%$ per year (obese BMI group).

**Table III** presents unadjusted and adjusted comparisons of annual percent change in eGFR for those with multiple CMRFs or MetS compared with children with normal BMI and no multiple CMRFs. The group with normal BMI and without multiple CMRFs over 2 years (considered lowest risk) was used as the reference for the analyses described in **Table III**. For this group, the average annual percent change in eGFR was $-3.19\%$ (95% CI $-4.11\%$, $-2.27\%$). Those who had a normal BMI and incident multiple CMRFs had a faster decline of eGFR (annual change $-5.62\%$, $P$ for difference with reference group $= .044$). Those with persistent MetS had an eGFR change of $-6.18\%$ per year (95% CI $-8.48\%$, $-3.83\%$) and this was also a significantly faster decline than the reference group ($P$ for difference $= .020$). Those with incident and resolved MetS also had faster eGFR declines (estimated annual percent change $= -5.11\%$ and $-5.89\%$, respectively), but these estimates were not significantly different from the reference group ($P = .231$ and .208, respectively). In adjusted models, those who had normal BMI and incident multiple CMRFs had a faster decline of eGFR compared with children who never had multiple CMRFs ($-6.33\%$ vs $-3.38\%$, $P = .048$). Among children who were overweight or obese, those with persistent MetS had the fastest GFR decline ($6.08\%$ per year), a value that was significantly different from the reference group ($P = .036$). Those with incident or resolved MetS also experienced a faster estimated GFR decline compared with the reference group, but these differences were not statistically significant.

To characterize the relationship between these MetS categories and the prevalence of fast progression defined as an eGFR decline of greater than 10% per year, a binary outcome was defined (represented as the shaded portions in **Figure 2**) and used in logistic regression models presented in **Table III**. In unadjusted analyses, those with a normal BMI and incident or resolved multiple CMRFs had about 2 times greater odds of fast progression compared with the reference group ($P = .016$ and .013). Children with a normal BMI and persistent multiple CMRFs also had greater odds of fast eGFR decline compared with the reference group ($P = .056$). In unadjusted analyses, among children with a greater BMI, those with incident, persistent, or resolved MetS were more likely to have a fast (>10%) eGFR decline than the reference group (OR = 2.30, 2.12, and 1.94, respectively). In adjusted analyses, the associated were similar: all the comparison groups had greater odds of a fast eGFR decline than the reference group, and the differences reached significance for children with a normal BMI and with incident or resolved multiple CMRFs, or children with an elevated BMI and with persistent MetS but not incident or resolved MetS.

## Discussion

Our study demonstrated that about one-half of the CKiD participants who were overweight or obese had multiple CMRFs and met criteria for MetS and that the prevalence of MetS/multiple CMRFs was associated with a faster decline of kidney function. A greater prevalence of MetS in children with CKD
compared with the general population of children is not surprising in the context of a high prevalence of individual traditional cardiovascular risk factors (ie, hypertension, dyslipidemia, hyperglycemia/insulin resistance) seen in this population. The frequency of MetS in our study was similar to that of adults with CKD, a population with a high frequency of diabetes, hypertension, and pre-existing cardiovascular disease. These results are important because MetS in adults with CKD is associated with increased cardiovascular morbidity and mortality. In children, the presence of multiple CMRFs is associated with early atherosclerosis as is evident from noninvasive and autopsy studies in children.

Children who had MetS at their initial visit were more likely to continue to have MetS subsequently. This group with persistent MetS had the fastest rate of CKD progression. The common theory for worsening of CKD in the presence of MetS...
is attributed partly to specific CMRFs (hypertension and insulin resistance, in particular). However, previous studies have shown that obesity is independently associated with the development and progression of CKD, including those patients without diabetes and hypertension, 2,3,10-12 suggesting that metabolically healthy but obese patients have an increased risk of CKD.19,20 This is also supported by pathologic changes, including glomerular sclerosis, tubular atrophy, and interstitial fibrosis found in patients with severe obesity and the MetS.

Although a greater frequency of MetS in children who are overweight or obese is expected, we also found that approximately one-third of the CKD participants with a normal weight had ≥2 CMRFs (nonobese but metabolically unhealthy group). More importantly, participants with multiple CMRFs in both the normal and high BMI categories had a consistently faster decline in kidney function compared with those who had no history of multiple CMRFs. These findings suggest that the presence of multiple CMRFs rather than obesity per se might be more important for CKD progression in our cohort. However, because the prevalence of multiple CMRFs was significantly greater in a group of overweight and obese children vs the normal-weight group, children with obesity should still be considered as a high-risk group for CKD progression.

We also observed that those with resolved multiple CMRFs experienced an accelerated decline in eGFR compared with those who never developed multiple CMRFs (Table III). This suggests that the risk conferred during the time when multiple CMRFs were present continued even after the observed resolution. It should be noted that the time frame of this analysis was approximately 2 years and that the change in multiple CMRFs and eGFR decline should be interpreted in that context. It is possible that longer follow-up may divulge longer-term benefits related to CMRF resolution.

Our study has important strengths, including a large sample size and standardized demographic, clinical, and laboratory measurements over time. Our definition of “MetS,” although consistent with Adult Treatment Panel III criteria, has an exception that instead of using any 3 of 5 CMRFs, we have divided groups using BMI as a consistent variable as recommended by an Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents.4 This allowed us to compare the presence and effects of multiple CMRFs in the normal BMI group with those that are overweight or obese and have multiple CMRFs. We have included BMI instead of waist circumference as a measure of obesity because BMI has discriminated cardiovascular risks among adolescents in a previous study23 and offered robust associations with cardiometabolic variables.24

However, there are limitations to our study. Because our primary aim was investigating pediatric MetS, our analysis described the burden of conditions as a total count such that each condition is given equal weight. This is limitation as specific comorbidities to define MetS (eg, hypertension, dyslipidemia, or abnormal glucose metabolism) may confer different levels of risk. However, there is no currently established hierarchy that describes the potentially different levels of risk. Future research should investigate how each component of MetS is related to risk, because it is not likely that each condition confers an equal risk. Identifying risk contribution and clustering of variables will help clinicians prioritize treatment for children with MetS. Although the eGFR in our study was calculated using

| Table III. Comparing pairs of person visits in children ever developed MetS to those who never developed MetS |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Adjustments | Never ≥2 CMRFs | Incident ≥2 CMRFs | Resolved ≥2 CMRFs | Persistent ≥2 CMRFs | Never MetS | Incident MetS | Resolved MetS | Persistent MetS |
| Annual percent change of eGFR | | | | | | | | |
| Unadjusted Estimate | -3.19 | -5.62 | -5.41 | -6.40 | -4.56 | -5.11 | -5.89 | -6.18 |
| P value | Ref. | .044 | .092 | .032 | .204 | .231 | .206 | .020 |
| Adjusted Estimate | -3.38 | -6.33 | -5.42 | -6.46 | -4.53 | -4.84 | -5.44 | -6.08 |
| P value | Ref. | .048 | .123 | .045 | .325 | .368 | .406 | .036 |
| Fast decline of eGFR (annual percent decline >10) | | | | | | | | |
| Unadjusted Estimate | 1 | 2.06 | 1.98 | 1.81 | 2.06 | 2.30 | 1.94 | 2.12 |
| 95% CI | (1.15, 3.69) | (1.15, 3.41) | (0.98, 3.32) | (0.47, 1.87) | (1.09, 4.83) | (0.94, 3.99) | (1.18, 3.81) | (0.86, 3.85) |
| P value | Ref. | .016 | .013 | .056 | .062 | .028 | .071 | .012 |
| Adjusted Estimate | 1 | 2.13 | 1.86 | 1.76 | 1.07 | 2.03 | 1.81 | 2.11 |
| 95% CI | (1.15, 3.94) | (1.07, 3.24) | (0.94, 3.30) | (0.51, 2.28) | (0.92, 4.49) | (0.86, 3.85) | (1.13, 3.95) | (0.86, 3.85) |
| P value | Ref. | .016 | .028 | .076 | .852 | .080 | .121 | .019 |

NA, not available.
*Adjusted for CKD diagnosis, maternal education, sex, race, CKD duration (in years), and corticosteroid use.
combined serum creatinine and cystatin C by the CKiD estimating equation, we cannot exclude that the performance of eGFR was affected by obesity. Creatinine-based equations have demonstrated significant variability among patients who are obese. There are studies suggesting that cystatin C–based formulas may provide a more accurate kidney function estimation irrespective of body composition; however, others argue that cystatin C might underestimate eGFR, especially in obese populations.

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