The Impact of Short Stature on HRQoL in Children with Chronic Kidney Disease

Amira Al-Uzri, MD, MCR[1,*], **Matthew Matheson, MS**[2], **Debbie S. Gipson, MD**[3], **Susan R. Mendley, MD**[4], **Stephen R. Hooper, Ph.D**[5], **Ora Yadin, MD**[6], **David Rozansky, MD, Ph.D**[1], **Marva Moxey-Mims, MD**[7], **Susan L. Furth, MD**[8], **Bradley A. Warady, MD**[9], and **Arlene C Gerson, Ph.D**[10] **on behalf of the Chronic Kidney Disease in Children Study Group**[*]

[1]Oregon Health & Science University

[2]Johns Hopkins University School of Public Health

[3]Univeristy of Michigan

[4]University of Maryland School of Medicine

[5]University of North Carolina School of Medicine

[6]University of California in Los Angeles

[7]National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health

[8]Children's Hospital of Philadelphia

[9]Children's Mercy Hospitals and Clinics

[10]Johns Hopkins University School of Medicine

Abstract

Objectives—To compare the health-related quality of life (HRQoL) of children with CKD and short stature (SS) to children with CKD and normal height (NH), to evaluate the impact of catch up growth and growth hormone use on HRQoL, and to describe the concordance of perceptions of HRQoL between children with SS and NH and their parents.

Study design—483 children and/or parents enrolled in the multicenter CKiD study and had completed the Pediatric Quality of Life Inventory (PedsQL, V4.0) on at least two CKiD study visits comprised this sub-study population. Participants were dichotomized into NH or SS groups. The demographic characteristics that varied at baseline (sex, GFR and parent education) were

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*Corresponding author: Amira Al-Uzri, M.D., MCR., Associate Professor, Pediatrics, Oregon Health & Science University, Department of Pediatrics, Division of Pediatric Kidney Services and Hypertension, 707 SW Gaines Road-CDRCP, Portland, OR 97239, Phone: 503-494-7327, Fax: 503-418-6718, aluzria@ohsu.edu.
*A list of members of the Chronic Kidney Disease in Children (CKiD) Study Group is available at www.jpeds.com (Appendix).

controlled for in the main analysis evaluating the impact of catch up growth and use of growth hormone on HRQoL.

Results—Multivariate modeling (controlling for confounding variables) revealed a significant association between both catch up growth and growth hormone usage on parent-proxy reports of child physical functioning (p<.05) and social functioning (p<.05). Older children with CKD (15 to 17 years old) had significantly higher ratings than their parents on PedsQL Physical, Emotional, Social and School Functioning scales compared with younger children (8–14 years old).

Conclusion—The finding that height gains and growth hormone use are associated with increases in physical and social functioning by parent report provides additional support for interventions to improve height in children with CKD. The importance of evaluating both the parent and child perceptions of HRQoL is supported by our results.

Short stature (SS) is common in children with chronic kidney disease (CKD) due to multiple factors (1). A study published by the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reported that 36 % of children with CKD had height Z score < -1.88 at time of enrollment (5).

Research evidence in non-CKD populations demonstrates that taller stature is equated with better health, better income (6, 7), more social opportunities, and fewer behavioral problems (8, 9). In addition, published research in non-CKD populations has reported that compared with children with NH, children with SS have poorer school performance (10, 11), lower self-esteem, difficulties with adaptation, teasing in school and juvenilization (12, 13). It is also important to point out that some research with children has not observed a relationship between height and various aspects of HRQoL.

Recent evidence points to the impact of chronic kidney disease on HRQoL. For example, cross-sectional data demonstrated that children with CKD to have lower HRQoL scores compared with healthy children (14). Of particular relevance to the present study was the findings that children with SS (less than the 5th percentile corrected for age) had twice the odds of having impaired HRQoL compared with children with CKD and normal height (14).

One of the common methodological criticisms of previously published pediatric HRQoL research is the use of a single informant (i.e. either parent or child). Observations of parent-child disagreement about HRQoL, particularly prominent in adolescent populations, have led to endorsement of multi-informant ratings of HRQoL (15, 16).

This report expands on previously published research evaluating the association between height and HRQoL in children with CKD using a longitudinal data set. The aims of this study were threefold: (1) to compare the HRQoL of children with mild to moderate CKD and SS with that of children with CKD and NH; (2) to evaluate the impact of increases in height and growth hormone use on HRQoL; and (3) to investigate the concordance of parent and child perceptions of HRQoL in children with SS and NH.

Methods

This study uses data collected in the multicenter CKiD study. The CKiD study design and objectives have been previously described (17). In brief, CKiD is a prospective, longitudinal, observational study of children with CKD who are enrolled at ages 1–16 years. The study protocol includes periodic assessments of HRQoL of children ages 8 years and older and their parents. This study is comprised of 483 children who were recruited into CKiD and who had at least two evaluations of their HRQoL. Height and HRQoL data were collected at approximately six months, one year, and two years after study entry. The CKiD study was approved by the Institutional Review Board of each participating clinical site.

All children had mild to moderate CKD with an estimated glomerular filtration rate ranging between 30–90 ml/min/1.73m^2 calculated by the Schwartz formula at study enrollment (18). Height was measured at all study visits using a stadiometer in all children > 2 years who can stand and length was measured in children who are unable to stand by using a firm box in the supine position (17). The subjects in this study were dichotomously divided into the short stature or normal height group. Short stature is defined as having a height less than or equal to the 3rd percentile for age and sex, corresponding to a height Z score of −1.88 or lower at the time of study enrollment. Children who did not fit the definition of SS were considered to have normal height for their age and sex. The SS definition used in this report matches the criteria used by the FDA in approving growth hormone therapy in children with CKD as well as in efficacy trials of growth hormone for children with CKD and SS (19). Kidney function was measured at the initial study visit using the plasma disappearance of iohexol (iGFR) (18).

The 23-item Pediatric Quality of Life Inventory (PedsQL™, Version 4.0) (20) was used to evaluate HRQoL. The PedsQL assesses the problem frequency within the domains of physical, emotional, social, and school functioning. Responses for items on the PedQL are summed and transformed into a score ranging from 0–100. Higher scores suggest a better HRQoL. All parents filled out the parent-proxy version of PedsQL. Parents of children older than 8 years and their child completed age-specific forms. Some of the analyses reported below used parent/child dyad data, and other analyses were not restricted in this manner.

Statistical Analyses

The main outcome in this study was HRQoL measured using the PedsQL Overall score and scores for each of the four PedsQL subscales (Physical Functioning, Social Functioning, Emotional Functioning, and School Functioning). Baseline HRQoL was measured at the second (6 months) CKiD study visit. Confounding variables were identified using two-sample t-tests. Next, univariate relationships between groups (SS and NH) and HRQoL, but not controlling for confounding variables, were computed. Additionally, within each stature group, we used t-tests to compare HRQoL between children on GH therapy and children not on GH (p-values less than 0.05 were considered to be statistically significant).

For the second research question we conducted longitudinal analyses incorporating height data from visits at six months (baseline), one year, and two years after study entry. A simple mixed model linear regression was used to assess whether height Z-score increased over time, particularly in those with SS at baseline. For this analysis the only predictor variable was short stature at baseline and the outcome variable was height Z-score.

To determine the strength of the longitudinal relationship between height and HRQoL, a multivariate mixed model regression approach was used to examine the relationship between height Z-score and HRQoL among only the children with SS at baseline, accounting for repeated measures and adjusting for growth hormone use at baseline, age, sex, maternal education and ieGFR. Due to the fact that iohexol-based GFR is not measured at all visits, estimated GFR (eGFR) is calculated when iGFR is not available to complete the longitudinal data; ieGFR is defined as iGFR if it is available, eGFR if it is not. This analysis allowed us to assess whether catch-up growth in children with SS affected their HRQoL while controlling for potential confounders.

To assess for an effect of GH therapy on HRQoL, GH was considered a separate predictor variable, not merely a surrogate marker for height within the mixed model regression analysis.

Our final analysis evaluated agreement in ratings in all domains between parent and child HRQoL. A longitudinal mixed model regression method specifically designed to evaluate concordance between two raters was used. The model estimates correlation; bias, defined as average difference between child and parent rating; and the difference in dispersion of scores within groups (defined as the ratio of the standard deviations). Necessarily, we restricted this analysis to parent-child dyads with HRQoL scores. We examined agreement separately for children less than 15 years old versus 15 or older. We considered fifteen years as representing mid-adolescence that defines the start of the transitioning phase into adulthood (21, 22) during high school years.

These analyses were conducted using SAS version 9.2.

Results

The age range of children in this study at baseline was 2 to 17 years and was 3–18 years at the time of analysis. Of the 483 subjects, 297 (61.5%) were males and 71 (15%) had SS at baseline. Among children with SS, only 17 (24%) were on GH. Among children with NH, 41 (10%) were on GH therapy.

The two groups were comparable at baseline in all characteristics except sex, iGFR, and maternal education. Compared with the SS group, a higher percentage of males, a higher iGFR, and higher maternal education were observed in the NH group (Table I).

Comparison of Patients with CKD with and without Short Stature

The mean scores for each domain for PedsQL completed by parents and children are displayed in Table II. Univariate group comparisons suggested that parent-reported physical HRQoL was lower in the SS group compared with the NH group but the difference did not reach statistical significance (p=.054). The effect size for this group difference is in the small to moderate range (Cohen d =.315).

Longitudinal Analysis of Growth and HRQoL

Longitudinal analysis of growth was performed after excluding six subjects whose growth patterns suggested measurement errors (ie, substantial decline in height, growing then shrinking, or shrinking then growing). The results of this analysis indicated that children with SS at baseline had a positive change in their height Z score over time (p <0.0001) indicating significant growth, and those with NH did not show significant change in their height Z- score (p >.05).

When assessing whether catch-up growth in children with SS was associated with improvements in HRQoL, increase in height Z-score (controlling for use of growth hormone, sex, child age, ieGFR and maternal education) was significantly associated with an approximate 7 point increase in PedsQL parent-proxy perception of physical functioning and social functioning of children. Conversely, no significant association between catch up growth and improvement in HRQoL was seen with analyses of child-completed PedsQL data (Table III). Other findings of this analysis include the observation that child age was inversely associated with parent observations of their child's physical, emotional, social, school and overall HRQoL (Table III). In order to evaluate potential age-related bias we conducted an analysis of PedsQL data from Parent/Child dyads. We observed that the trends in parent reported HRQoL domain scores remained significant for physical domain (p=0.03), yet others did not reach statistical significance when compared with all-age parent HRQoL scores (data not presented).

Growth Hormone use

When the two groups were further subdivided into those taking versus not taking growth hormone, there were a total of 58 children on GH therapy in the study population (12% of study sample). Univariate relationships were not observed in any of the PedsQL subscales among those who were on GH therapy compared with those who were not on GH within each stature group (data not shown). Alternatively, multivariate modeling confirmed a significant impact of improved height Z- score with growth hormone usage on parent-reported physical functioning (p<.05) as well as social functioning (p<.05) of their children (Table III).

Parent and Child Agreement on HRQoL Ratings

The analysis of agreement between parent and child ratings on the PedsQL subscales was performed for parent-child dyads of younger (8–14 years) versus older children (15–17 years) (Table IV). This analysis showed a statistically and clinically important discordance between the parent and child PedsQL scores in the older adolescents, with this group of patients reporting significantly higher scores than their parents in all PedsQL domains except school performance. In addition, the analysis showed a wider dispersion in the parent PedsQL scores compared with teen scores in the adolescent group. In comparison, a high level of concordance between parent and child PedsQL scores was observed in the younger group, except in the emotional functioning subscale. On average, younger children rated their emotional functioning worse than did their parents. Similar to the older adolescent group, there was a larger dispersion in the parent versus child scores.

Discussion

The use of GH is not a universally accepted clinical practice in children with CKD(23) despite the positive effect of GH therapy on height (24). It has been speculated that the absence of research demonstrating a definitive difference in the HRQoL of children with SS and NH, as well as the absence of research demonstrating that improvements in height are associated with improvements in HRQoL has hindered the widespread use of GH treatment of children with SS (5, 12, 23). The present study sought to provide some empirical support for the relationship between improved height and improved HRQoL in youth who have mild to moderate CKD. One of the study's strengths is the use of a longitudinal data set with a large cohort of children. These study design factors allowed for an unprecedented characterization of the relationship between growth and HRQoL in children with CKD over a period of several years.

We know from a previous publication based on data from the CKiD study that children with CKD have lower HRQoL scores compared with healthy children and that children with SS and CKD had double the odds of a more impaired HRQoL (14). The association between height and HRQoL was replicated and extended in the present study using a more stringent criterion to define SS (less than the 3rd percentile corrected for age and sex) and a longitudinal data set.

With regard to the demographics of our study population, we found a lower percentage of males among the SS group compared with the NH group. This finding may reflect sex bias in favor of boys that had been reported previously in children referred for treatment with growth hormone (25, 26). We also found a lower iGFR in children with SS compared with NH with a mean difference of 7.8 ml/min|1.73m^2. This finding is similar to previous reports that show poorer growth in association with lower GFR (27). In addition, maternal education differences were observed, with mothers of children in the NH group displaying higher educational achievement than mothers of children in SS group. This new finding in children

with CKD and SS is in contrast to a published report about the lack of difference in maternal education between children with SS versus NH in the general population (28). Differences in population characteristics and cause of SS may account for the different results observed in our study. Even after controlling for the aforementioned confounding variables, support for the association between height gains and HRQoL improvement was observed.

Our data show significant associations between improvement in height Z-scores and better HRQoL scores in the physical functioning and social functioning domains by parent proxy. Our interpretation of this finding is that parents of children with SS consider the physical and social functioning to be similarly impacted by growth.

This finding also provides support for including HRQoL in clinical decision making regarding the initiation of growth hormone therapy in children with CKD and SS. In comparison with parent attributions of height gains and improved HRQoL, children with height gains (improved Z-scores) did not report concomitant improvements in ratings of their HRQoL. These discrepant results can be interpreted in a variety of ways. Some are inclined to conclude that HRQoL is more important/valid if assessed by parents rather than children. Others may interpret this finding to support adherence with the recent recommendations to query both parents and children when evaluating the quality of life of children with chronic medical problems so as to obtain the most comprehensive assessment (15, 16). Alternatively, this finding may be dismissed as a statistical artifact that results from higher child reported PedsQL scores at baseline.

Consistent with previously published studies, concordance of youth and parent perceptions of HRQoL were age dependent (15). Our study observed a lower correlation between self and parent proxy PedsQL scores related to physical functioning, emotional functioning and social functioning among adolescents compared with younger patients with CKD. Parent ratings of their adolescent's physical, emotional, and social functioning were lower than adolescent ratings of the same aspects of HRQoL. These findings may signify increased parent concern regarding the long-term impact of CKD on HRQoL. Conversely, adolescents may not share their parents' worry (15, 16). These findings provide additional support for the importance of ongoing assessment of HRQoL in children with both SS and NH from both parental and youth perspectives.

The finding that a large number of children with SS are not receiving GH therapy (76%) concurs with previous reports about the low utilization of GH in children with CKD (5). Early referral for kidney transplantation, financial burden of GH therapy, the requirement for daily injection, and the parent's concern of long-term side effects may all play a role in parental decisions regarding GH use.

It is important to point out several study characteristics that may limit the generalizability of the findings. First, the relatively small number of children on GH therapy may have limited our ability to detect any differences in the HRQoL scores between those with SS and those with NH. Second, a two year follow-up may not be sufficient to reliably determine the type and magnitude of the relationship between height improvements and HRQoL. Lastly, the use of a generic HRQoL instrument may not be as sensitive in detecting changes in HRQoL as a disease-specific HRQoL instrument (29).

In summary, the finding that height gains in children with SS and CKD are associated with parent perception of youth HRQoL in the domains of physical and social functioning provide additional support for interventions that are likely to optimize final height in this population, including earlier use of GH therapy. Sharing these study findings with parents of children with CKD and SS may improve parent acceptance of physicians' recommendations

for GH therapy. Sharing these study findings with health care providers may change care practice.

Acknowledgments

Key words

HRQoL	Health Related Quality of Life
CKD	Chronic kidney disease
CKiD	Chronic Kidney Disease in Children
GH	Growth hormone
SS	Short stature
NH	Normal height

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Appendix. List of CKiD sites and principal investigator by CCC

Midwest Clinical Coordinating Center Principal Investigator: Bradley Warady, MD

Sites	Principal Investigator
British Columbia Children's Hospital	Colin White, MD, FRCPC, FAAP
Cardinal Glennon Hospital	Ellen Wood, MD
Children's Hospital of Alabama	Sahar Fathallah, MD

Sites	Principal Investigator
Children's Hospital of Boston	Nancy Rodig, MD[a]; William Harmon, MD
Children's Hospital of Los Angeles	Gary Lerner, MD
Children's Hospital of Winnipeg	Tom Blydt-Hansen, MD
Children's Kidney Specialists, Idaho	Randall Jenkins, MD
Children's Mercy Hospital, Kansas City	Bradley Warady, MD
Cincinnati Children's Hospital and Medical Center	Jens Goebel, MD[a], Mark Mitsnefes, MD
Egleston Children's Hospital, Emory University	Larry Greenbaum, MD, PhD
LeBonheur Children's Medical Center	Colleen Hastings, MD
Medical College of Wisconsin	Cynthia Pan, MD
Northwest Pediatric Kidney Specialist	Randy Jenkins, MD
Oklahoma University Health Sciences Center	Martin Turman, MD, PhD
Oregon Health and Science University	Amira Al-Uzri, MD[a]; Randall Jenkins, MD
Phoenix Children's Hospital	Bruce Morgenstern, MD
Rainbow Babies and Children's Hospital	Katherine Dell, MD
Seattle Children's Hospital	Joseph Flynn, MD
St. Louis Children's Hospital	S. Paul Hmiel, MD
Stanford University Medical Center	Cynthia Wong, MD[a]; Steven Alexander, MD
UCSF Children's Hospital	Anthony Portale, MD
University of California, Los Angeles	Isidro Salusky, MD; Ora Yadin, Md[a]
University of California, San Diego	Nadine Benador, MD[a]; Robert Mak, MD, PhD
University of New Mexico Children's Hospital	Craig Wong, MD
University of Texas Southwestern Medical Center	Mouin Seikaly, MD
University of Wisconsin	Sharon Bartosh, MD
Vanderbilt University Medical Center	Deborah Jones, MD

East Coast Clinical Coordinating Center Principal Investigator: Susan Furth, MD, PhD

Sites	Principal Investigator
Ann & Robert H. Lurie Children's Hospital of Chicago	Craig Langman, MD
Carolinas Medical Center	Susan Massengill, MD
Children's Hospital at Montefiore	Frederick Kaskel, MD, PhD
Children's Hospital of Michigan	Tej Matoo, MD
Children's National Medical Center	Kanwal Kher, MD
Children's Hospital of Philadelphia	Susan Furth, MD, PhD
DeVos Children's Hospital at Spectrum	Yi Cai, MD[a]
East Carolina University	Guillermo Hidalgo, MD
Hospital for Sick Children (Sick Kids)	Rulan Parekh, MD[a]; Lisa Robinson, MD
INOVA Fairfax Hospital for Children	Lauren Weintraub, MD
Johns Hopkins Children's Center	Meredith Atkinson, MD
Maimonides Medical Center	Juan Kupferman, MD
Maria Fareri Children's Hospital at Westchester Medical Center	Dmitry Samsonov, MD

Sites	Principal Investigator
Mount Sinai Medical Center	Jeffrey Saland, MD
Nationwide Children's Hospital, Ohio State Univ.	Hiren Patel, MD
Riley Hospital for Children at Indiana University Health	Sharon Andreoli, MD, PhD
Robert Wood Johnson Medical School – UMDNJ	Lynne Weiss, MD
SUNY Downstate Medical Center	Anil Mongia, MD
Texas Children's Hospital, Baylor	Poyyapakkam Srivaths, MD
University of Florida	Richard Neiberger, MD
University of Illinois, Chicago	Eunice John, MD
University of Iowa	Patrick Brophy, MD
University of Maryland	Susan Mendley, MD
University of Michigan, Mott Hospital	Debbie Gipson, MD[a]
University of North Carolina, Chapel Hill	Maria Ferris, MD
University of Rochester Medical Center, Golisano Children's Hospital at Strong	Marc Lande, MD[a], George Schwartz, MD
University of Texas, Houston	Joshua Samuels, MD
University of Virginia	Victoria Norwood, MD

[a]Clinical Site Principal Investigator

Table 1

Demographics of participants at baseline.

Characteristic	Short Stature (SS) (N=71)	Normal Height (NH) (N=412)
Age (y) mean ± SD	10.37 ± 4.47	11.28 ± 4.31
Age < 8 years	23 (32%)	98 (24%)
Male [*]	36 (51%)	261 (63%)
African-American race	12 (17%)	84 (20%)
Hispanic ethnicity	12 (17%)	61 (15%)
Maternal Education [*]		
High School or Less	38 (56%)	163 (40%)
Some College	16 (24%)	114 (28%)
College or More	14 (21%)	128 (32%)
iGFR (ml/min|1.73m^2) [*] mean ± SD	40.03 ± 17.48	47.83 ± 18.19
Glomerular CKD etiology	16 (23%)	94 (23%)

[*]
$p < 0.05$ for difference between groups.

Table 2

The mean scores for the parent and child reports of HRQoL in children with short stature (SS) and those with normal height (NH)

Rater	HRQoL measure	Number of children (SS, NH)	Children with CKD and SS	Children with CKD and NH	Normative values from Varni (20)
Parent	Physical	69, 399	72.70 ± 24.09 [*]	79.01 ± 20.92 [*]	83.26 ± 19.98
	Emotional	69, 398	73.49 ± 16.62	74.52 ± 18.28	80.28 ± 16.99
	Social	69, 398	73.99 ± 23.02	78.99 ± 21.10	82.15 ± 20.08
	School	66, 379	63.65 ± 22.14	65.37 ± 21.47	76.91 ± 20.16
	Overall	69, 399	71.36 ± 17.92	75.29 ± 16.85	81.34 ± 15.92
Child	Physical	45, 304	78.33 ± 18.63	80.20 ± 15.50	86.86 ± 13.88
	Emotional	45, 304	73.78 ± 19.54	73.46 ± 17.96	78.21 ± 18.64
	Social	45, 304	78.69 ± 22.63	80.79 ± 18.69	84.04 ± 17.43
	School	45, 304	62.18 ± 20.49	64.42 ± 18.13	79.92 ± 16.93
	Overall	45, 304	73.89 ± 15.31	75.41 ± 14.07	82.87 ± 13.16

No significant differences (all *p*>0.05) were observed between SS and NH groups and between those on or off GH therapy among the SS group or the NH group.

[*] *p* = .054 for the comparison of Parent-reported Physical HRQoL between SS and NH subjects.

Table 3

Linear mixed model results (regression coefficients and 95% confidence intervals) for HRQoL with data from 6-month, 1-year, and 2-year follow-up visits on children with short stature at baseline (N=65; six children with abnormal growth patterns removed).

	HRQoL Scale (Parent Ratings)				
Covariate	*Physical*	*Emotional*	*Social*	*School*	*Overall*
Height Z-score	7.33 * (0.92, 13.74)	−0.29 (−5.72, 5.14)	7.54 * (1.34, 13.74)	2.93 (−4.04, 9.90)	4.34 (−0.63, 9.31)
Growth hormone	9.66 * (0.24, 19.08)	−0.30 (−8.04, 7.44)	9.52 * (0.44, 18.60)	0.35 (−10.20, 10.91)	5.57 (−1.95, 13.08)
Male sex	−0.70 (−8.94, 7.53)	−0.13 (−6.89, 6.63)	−2.92 (−10.86, 5.02)	−2.03 (−11.13, 7.08)	−1.36 (−7.95, 5.22)
Age	−0.89 (−1.80, 0.03)	−0.91 * (−1.66, −0.16)	−1.11 * (−1.99, −0.23)	−1.38 * (−2.40, −0.37)	−1.09 * (−1.82, −0.37)
ieGFR	0.26 * (0.05, 0.48)	−0.04 (−0.22, 0.14)	0.14 (−0.07, 0.34)	0.27 * (0.05, 0.50)	0.16 (0.00, 0.33)
ME: Some college[a]	0.88 (−9.73, 11.49)	−6.31 (−15.05, 2.44)	−4.97 (−15.20, 5.27)	−4.24 (−15.99, 7.51)	−2.79 (−11.25, 5.67)
ME: College or more[b]	7.42 (−2.42, 17.26)	1.97 (−6.06, 10.00)	6.29 (−3.19, 15.77)	6.84 (−4.16, 17.85)	6.32 (−1.58, 14.23)

	HRQoL Scale (Child Ratings)				
Covariate	*Physical*	*Emotional*	*Social*	*School*	*Overall*
Height Z-score	−1.70 (−8.66, 5.27)	−2.67 (−11.44, 6.10)	−5.04 (−14.51, 4.44)	0.64 (−7.98, 9.27)	−2.35 (−8.41, 3.72)
Growth hormone	4.69 (−4.77, 14.15)	4.61 (−6.38, 15.60)	7.15 (−4.74, 19.05)	3.55 (−7.05, 14.15)	4.61 (−3.41, 12.63)
Male gender	5.43 (−3.49, 14.35)	0.32 (−10.03, 10.68)	−2.66 (−13.86, 8.54)	−1.55 (−11.53, 8.43)	1.16 (−6.39, 8.72)
Age	−0.33 (−1.79, 1.12)	−0.32 (−2.09, 1.45)	1.21 (−0.71, 3.12)	0.15 (−1.58, 1.87)	0.15 (−1.10, 1.41)
ieGFR	0.29 * (0.08, 0.49)	0.24 (−0.02, 0.49)	0.13 (−0.15, 0.40)	0.17 (−0.08, 0.42)	0.20 * (0.03, 0.38)
ME: Some college[a]	4.82 (−6.93, 16.58)	−3.07 (−16.73, 10.58)	3.62 (−11.16, 18.40)	−2.63 (−15.80, 10.54)	1.20 (−8.76, 11.16)
ME: College or more[b]	14.03 * (3.81, 24.26)	4.68 (−7.07, 16.44)	14.16 * (1.44, 26.88)	17.14 * (5.84, 28.44)	12.67 * (4.03, 21.30)

[a] Maternal Education: Some college

[b] Maternal Education: College or more

* $p < 0.05$

Table 4

The assessment of agreement between parent and child QoL scores divided by age group using mixed model analysis.

HRQoL Scale	8–14 years old (N=921 visits)			15–17 years old (N=397 visits)		
	Bias[1]	SD Ratio[2]	Correlation[3]	Bias[1]	SD Ratio[2]	Correlation[3]
Overall	−0.35	0.81 *	0.81 **	4.23 **	0.73 *	0.73 **
Physical	0.42	0.76 *	0.75 **	5.28 **	0.74 *	0.66 **
Emotional	−2.59 *	0.92	0.67 **	3.03 *	0.98	0.59 **
Social	1.47	0.89	0.71 **	6.69 **	0.69 *	0.70 **
School	−1.13	0.77 *	0.82 **	1.16	0.78 *	0.72 **

[1] Bias indicates, on average, how the child's rating compares to the parent's rating. Positive bias indicates that the child rates higher than the parent in PedsQL points, negative indicates child generally rates lower than the parent in PedsQL points.

[2] SD Ratio is the estimated ratio of the standard deviations of the scores; it indicates the relative dispersion of the child scores versus the parent scores. A SD Ratio of 1 indicates equal "spread" of scores; a SD ratio of 0.7 would indicate that children have about 30% less variability in their scores than their parents.

[3] Correlation is a measure of between-rater agreement (parent versus child PedsQL scores) and can range from −1 to +1.

*
p<0.05.

**
p<0.0001.