

# Longitudinal assessment of the health-related quality of life of children and adolescents with chronic kidney disease

Chandana Guha<sup>1,2</sup>, Anita van Zwieten<sup>1,2</sup>, Rabia Khalid<sup>1,2</sup>, Siah Kim<sup>1,2</sup>, Amanda Walker<sup>3</sup>, Anna Francis<sup>4,5,6</sup>, Madeleine Didsbury<sup>1</sup>, Armando Teixeira-Pinto<sup>1,2</sup>, Belinda Barton<sup>7</sup>, Chanel Prestidge<sup>8</sup>, Emily Lancsar<sup>9</sup>, Fiona Mackie<sup>10,11</sup>, Joseph Kwon<sup>12</sup>, Kirsten Howard<sup>1,13</sup>, Kylie-Ann Mallitt<sup>1,2</sup>, Martin Howell<sup>1,2</sup>, Allison Tong<sup>1,2</sup>, Alison Hayes<sup>1</sup>, Rakhee Raghunandan<sup>1</sup>, Stavros Petrou<sup>12</sup>, Suncica Lah<sup>14</sup>, Steven McTaggart<sup>4,6</sup>, Jonathan C. Craig<sup>15,16</sup> and Germaine Wong<sup>1,2,16</sup>

<sup>1</sup>Sydney School of Public Health, The University of Sydney, Sydney, New South Wales, Australia; <sup>2</sup>Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, New South Wales, Australia; <sup>3</sup>Royal Children's Hospital, Melbourne, Victoria, Australia; <sup>4</sup>School of Medicine, University of Queensland, Brisbane, Queensland, Australia; <sup>5</sup>Centre for Kidney Disease Research, Translational Research Institute, Brisbane, Queensland, Australia; <sup>6</sup>Child and Adolescent Renal Service, Queensland Children's Hospital, Brisbane, Queensland, Australia; <sup>7</sup>The Children's Hospital at Westmead and Paediatrics and Child Health (CHERI), University of Sydney, Sydney, New South Wales, Australia; <sup>8</sup>Starship Children's Hospital, Auckland, New Zealand; <sup>9</sup>Department of Health Services Research and Policy, Australian National University, Canberra, Australian Capital Territory, Australia; <sup>10</sup>Sydney Children's Hospital, Randwick, Sydney, New South Wales, Australia; <sup>11</sup>School of Women's and Child Health, University of New South Wales, Sydney, New South Wales, Australia; <sup>12</sup>Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK; <sup>13</sup>Menzies Centre for Health Policy & Economics, School of Public Health, University of Sydney, Sydney, New South Wales, Australia; <sup>14</sup>School of Psychology, University of Sydney, Sydney, New South Wales, Australia; and <sup>15</sup>College of Medicine and Public Health, Flinders University, Adelaide, South Australia, Australia

In this multi-center longitudinal cohort study conducted in Australia and New Zealand, we assessed the trajectories of health-related quality of life (HRQoL) in children with chronic kidney disease (CKD) over time. A total of 377 children (aged 6-18 years) with CKD stages 1-5 (pre-dialysis), dialysis, or transplant, were followed biennially for four years. Multi Attribute Utility (MAU) scores of HRQoL were measured at baseline and at two and four years using the McMaster Health Utilities Index Mark 3 tool, a generic multi-attribute, preference-based system. A multivariable linear mixed model was used to assess the trajectories of HRQoL over time in 199 children with CKD stage 1-5, 43 children receiving dialysis and 135 kidney transplant recipients. An interaction between CKD stage at baseline and follow-up time indicated that the slopes of the HRQoL scores differed between children by CKD stage at inception. Over half of the cohort on dialysis at baseline had received a kidney transplant by the end of year four and the MAU scores of these children increased by a meaningful amount averaging 0.05 (95% confidence interval 0.01 to 0.09) per year in comparison to those who were transplant recipients at baseline. The mean difference between baseline and year two MAU scores was 0.09 (95% confidence interval -0.05, 0.23), (Cohen's d effect size 0.31). Thus, improvement

in HRQoL over time of children on dialysis at baseline was likely to have been driven by their transition from dialysis to transplantation. Additionally, children with CKD stage 1-5 and transplant recipients at baseline had no changes in their disease stage or treatment modality and experienced stable HRQoL over time.

Kidney International (2022) ■, ■-■; <https://doi.org/10.1016/j.kint.2022.09.026>

KEYWORDS: chronic kidney disease; health-related quality of life; health utilities index; pediatric nephrology

Copyright © 2022, International Society of Nephrology. Published by Elsevier Inc. All rights reserved.

Children with chronic kidney disease (CKD) frequently experience debilitating symptoms, including fatigue, nausea, poor appetite, and pain, and they have elevated risks of cognitive impairment, slow growth rates, and poorer psychosocial outcomes.<sup>1-4</sup> The improvements in health outcomes for children with other chronic diseases over the past decade have not translated to outcomes for children with advanced-stage CKD needing dialysis. Global data suggest that the mortality risk for children on dialysis is at least 30 times higher than that for their general-population peers.<sup>5</sup> Childhood CKD can negatively impact the physical, psychological, and social functioning of these children over their life course, and their quality of life into adulthood.<sup>6,7</sup>

Health-related quality of life (HRQoL) is a multidimensional concept that captures patient- or proxy-reported impact of disease and treatment on the patient's physical and psychosocial functioning.<sup>8</sup> Studies have shown that adults

**Correspondence:** Chandana Guha, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Sydney, NSW 2145, Australia. E-mail: [chandana.guha@sydney.edu.au](mailto:chandana.guha@sydney.edu.au)

<sup>16</sup>JCC and GW are co-senior authors.

Received 18 April 2022; revised 27 July 2022; accepted 1 September 2022

who had CKD during childhood find themselves at a considerable health, economic, and social disadvantage. They are likely to achieve fewer social milestones while growing up, and they experience low self-esteem, poor employment rates, fragile interpersonal relationships, and low rates of independent living as adults.<sup>6,9–11</sup> Findings from our previous study<sup>12</sup> indicate that, compared with healthy peers, children with CKD experience reduced HRQoL, driven largely by the domains of emotion, pain, and cognition. Factors associated with poorer HRQoL may include pain and poor emotional health for children on dialysis, cognitive impairment, short stature, and low socioeconomic status.<sup>1,2,6,13</sup> However, longitudinal information on the HRQoL of these children is sparse, as most of the existing studies are cross-sectional.<sup>2,14</sup>

An understanding is needed of the trajectory of HRQoL in children across the full spectrum of CKD and its association with the course of the disease, because knowledge of these changes over time will inform evaluation of potential interventions to improve patient-reported outcomes and care models. For the cohort of children with stage 15 CKD, receiving dialysis and being transplant recipients at baseline, this study aimed to describe the longitudinal changes in their preference-based HRQoL over time.

## METHODS

### Study population and design

The Kids with CKD (KCAD) study is a prospective longitudinal cohort study involving 377 children. All school-aged children with CKD (stages 1–5, on dialysis or with kidney transplants), aged between 6 and 18 years under the care of a pediatric renal service were invited to participate in the study. Participants were excluded if the caregivers were unable to provide written informed consent, or if the child was not receiving formal education. Children in families in which no one spoke English were also excluded. The children were enrolled from 5 (of 8) pediatric nephrology units across Australia and New Zealand, between January 2012 and September 2016, and were followed up biennially for up to 4 years. The cohort design and methods have been described previously.<sup>12</sup> The design, conduct, and reporting of the study are in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>15</sup>

This study was approved by the Human Research Ethics Committee (HREC) of all participating centers (The Children's Hospital at Westmead and Sydney Children's Hospital (HREC/12/SCHN/159), the Lady Cilento Children's Hospital (now known as the Queensland Children's Hospital; HREC/12/QCRH/113), the Royal Children's Hospital (Royal Children's Hospital Human Research Ethics Committee: 33229), and the Starship Children's Hospital (New Zealand Health and Disability Ethics Committees: 15/NTB/37). Written informed consent (or assent, depending on participant age) was obtained from all participants and/or caregivers.

### Cohort characteristics

Baseline characteristics of the children were obtained from caregivers and were cross-checked against medical records when relevant (for example, when values of CKD stage were missing). These included details of their medical history (cause of kidney disease, stage of kidney disease, comorbidities, medication, and immunosuppression)

and demographic data (age, sex, and ethnicity [Caucasian and non-Caucasian]) and socioeconomic status (SES). The SES of the family was represented by a global SES index including caregiver education, income, perceived financial status, employment status, and home ownership. Principal component analysis was used to determine a global index that includes multiple variables to provide a broader reflection of the socioeconomic inequalities in health experienced by this cohort. The indices derived were relative measures of SES within the cohort and were useful for considering inequality among the patients/households in the cohort. Principal component analysis was applied to all socioeconomic indicator variables (with > 10% contributions) to calculate a combined SES index score. The component with the highest eigenvalue (at least greater than 1) was used to specify the overall SES of the participants (global SES index). The SES component scores for participants were then categorized into quartiles, with the highest SES (highest quartile) assigned as the reference category.<sup>12</sup> The selection of covariates in our model was informed by evidence from published literature<sup>2,13,16</sup> and in consultation with experts in the field. The adjustment for the covariates was based on the conceptual directed acyclic graph, represented in [Supplementary Figure S1](#).

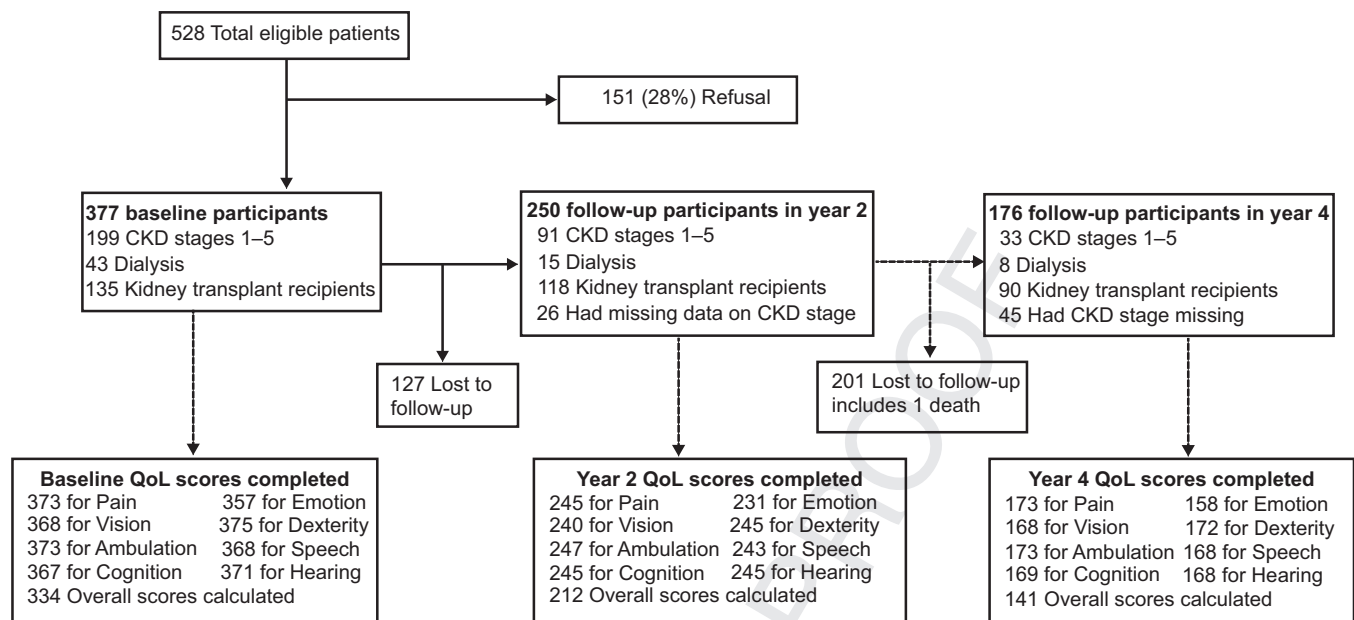
### Outcomes

HRQoL is measured using generic multi-attribute preference-based tools that are based on a health classification system underpinned by several dimensions or attributes. A multi-attribute utility (MAU) function provides a preference-based score for each of these health states.<sup>17,18</sup> The preference-based scoring system calculates the utility scores on a generic scale on which “dead” is scored as 0 and “perfect health” is scored as 1.

The generic multidimensional Health Utilities Index Mark 3 (HUI3) is a widely used, validated, preference-based measure and was used to assess the HRQoL of participants in this study. This MAU measure is based on single attributes of pain, hearing, speech, vision, dexterity, ambulation, cognition, and emotion; each with 5 or 6 levels of function.<sup>17</sup> This measure is also used extensively to assess the HRQoL of children aged 5 years and above, in the general population and in children with chronic illnesses<sup>17,19–21</sup>. This 40-item MAU instrument was completed by primary caregivers if their child was ≤ 8 years old<sup>13</sup> (or if an older participant could not complete the questionnaires themselves), or by the participant at the time of enrolment, and at 2 years and 4 years. Functions within each attribute were graded on a 5- or 6-point scale corresponding to level of severity, ranging from normal function (level 1) to severe impairment (levels 5 or 6).<sup>17</sup> The responses to the HUI3 health status classification system were converted into multiplicative MAU scores using a published utility function.<sup>13</sup> Single-attribute utility (SAU) scores were calculated from the ordinal scores using SAU functions. These MAU scores are based on the permutation of responses across the 8 attributes and are expressed on an interval scale ranging from −0.36 (representing the health state with the lowest level of function for all attributes) to 1.00 (representing the health state with the highest level of function for all attributes).<sup>17,18</sup>

### Statistical analysis

Demographic data are presented as frequencies (percentages) for categorical variables, and as median with interquartile range (IQR) for continuous variables. The MAU and SAU scores were non-normally distributed and were reported as median (IQR) and mean (with SD) for each CKD stage and the 3 different time periods (baseline, years 2 and 4), to enable the generation of utility estimates



**Figure 1 | Flow diagram of the study population.** Year 4 included 21 participants who were lost to follow-up in year 2 (21 participants with chronic kidney disease [CKD] stage recorded at baseline but missing in year 2). QoL, quality of life.

that can be used in other studies such as health economic evaluations.

To account for the repeated measurements within the individual participants and control for confounding effects, we used a multi-variable linear mixed model to assess the MAU and SAU scores over time in children with different CKD stages at study inception, adjusting for baseline covariates including age, sex, ethnicity, SES, and comorbidities (as fixed effects). A random intercept null model was fitted to check for clustering effects in the data.

Changes in the MAU scores during the study were calculated as the differences between baseline and follow-up measurements and were compared across the different stages of CKD using paired *t*-tests. Effect sizes were expressed by Cohen's *d* standardized effects by dividing the changes in each of the MAU scores by the pooled SD of that score estimated at baseline on the entire sample.<sup>22</sup> All analyses were carried out using R Studio Version 4.0.3.

## RESULTS

### Baseline characteristics of the cohort

A total of 377 children and adolescents (aged 6–18 years) were recruited from 2012 to 2016, with data collected at baseline, and at 2 and 4 years (Figure 1). Of the 377 children, 199 had CKD stages 1–5, 43 were on dialysis, and 135 had a functioning kidney transplant at study entry. The median age of the children was 12.6 years (IQR 6.6 years). The cohort comprised 62% (*n* = 233) males, and the majority were of Caucasian background (*n* = 220, 58%). Approximately 34% (*n* = 127) of the study cohort had congenital anomalies of the kidney and the urinary tract as the underlying cause of kidney disease. The baseline characteristics of the study population are presented in [Supplementary Table S1](#). Details of the missingness of the CKD stages and the HRQoL scores over time are provided in [Supplementary Table S2](#).

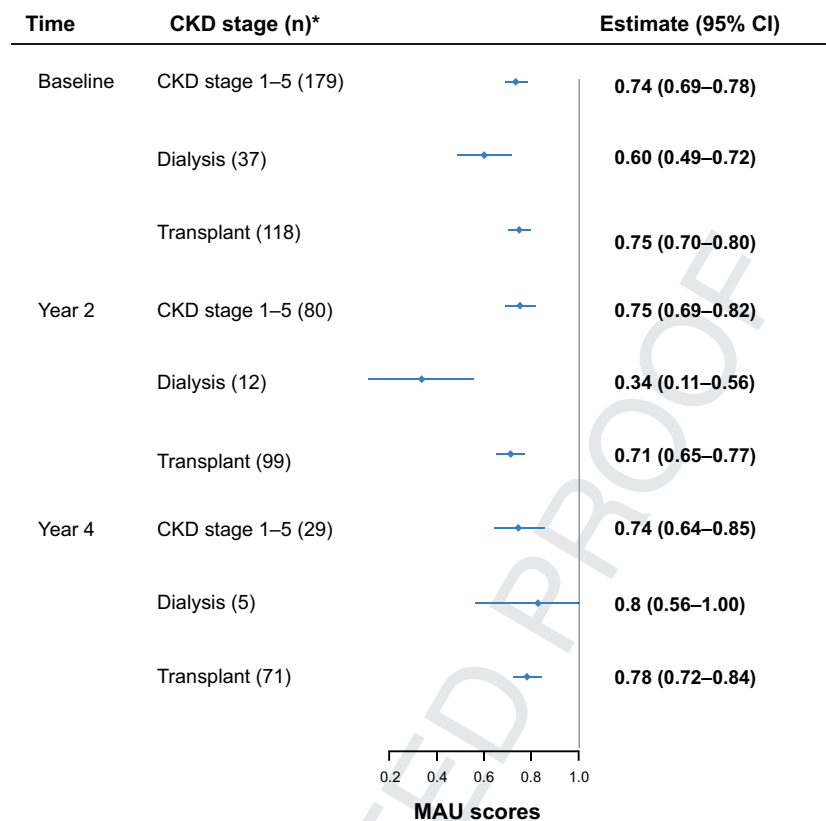
### Cross-sectional MAU scores at baseline, year 2, and year 4, stratified by CKD stages

The median and mean MAU scores are provided in [Supplementary Table S3](#). Figure 2 shows the distribution of the average MAU scores by CKD stage and at each time point. The mean (95% confidence interval [CI]) MAU scores for children on dialysis at baseline and year 2 were 0.60 (0.49–0.72) and 0.34 (0.11–0.56), respectively. The mean MAU scores for children with CKD stages 1–5 at baseline and year-2 follow-up were 0.74 (95% CI 0.69–0.78) and 0.75 (0.69–0.82), and transplant recipients had mean MAU scores of 0.75 (95% CI 0.70–0.80) at baseline and 0.71 (95% CI 0.65–0.77) at year 2. At the year-4 follow-up, very few children were on dialysis (*n* = 5). Details of the scores at year 4 are provided in Figure 2 and [Supplementary Table S3](#).

### Change in CKD stage over 4 years

The transition of participants between health states over the 3 time periods is shown in Figure 3. A total of 250 participants were followed for 2 years, and 224 recorded their CKD stage. Of the 224 children who were followed for year 2, 16 children (7%) treated with dialysis at baseline received a kidney transplant, 12 children (5%) with CKD (stage 5) at baseline received a kidney transplant, and 5 (2%) with CKD (stage 5) and 3 (1%) with a kidney transplant commenced dialysis.

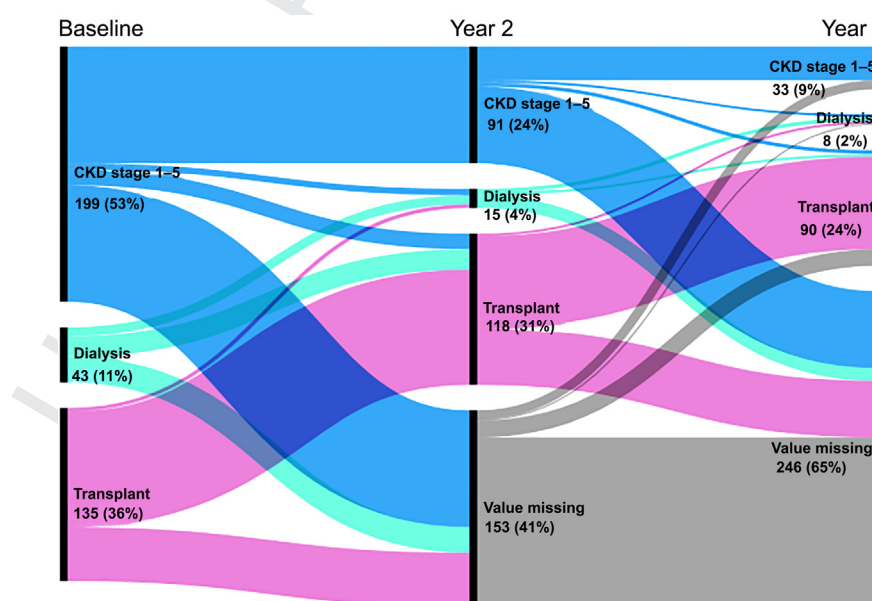
A total of 176 children were followed for up to 4 years, and data on the CKD stages of 131 participants were available. Two children (2%) with CKD (stage 1–5) and 2 (2%) with a kidney transplant at year 2 commenced dialysis by year 4, and 3 children (2%) with CKD (stage 5) in year 2 received a kidney transplant by year 4. An additional 2 children (2%) on dialysis at year 2 received a kidney transplant by year 4.



**Figure 2 | Cross-sectional assessments of the multi-attribute utility (MAU) scores of children with chronic kidney disease (CKD) stages at baseline, year 2, and year 4.** \*Number of patients whose CKD stage and multi-attribute utility (MAU) scores were available. CI, confidence interval.

The health state of most children who had early- or moderate-stage CKD or had a kidney transplant at baseline remained stable through the study period. Four patients (3%)

who were on dialysis and 2 (2%) with CKD stage 5 at baseline did not have follow-up data in year 2. These patients were subsequently followed and received a transplant by year 4.



**Figure 3 | Proportions of participants with changes in chronic kidney disease (CKD) stages over time.** Stages 1 and 2, and stages 3–5 patients have been grouped together for reporting purposes, but only those with stage-5 CKD received a transplant.



**Table 1 | Mixed model for MAU scores with interaction term between baseline CKD stage and follow-up time**

Variable	Estimate	95% CI	<i>p</i>
Intercept	0.77	0.68 to 0.86	<0.001
Time (per year of follow-up)	0.001	−0.01 to 0.02	0.93
Male	0.07	0.01 to 0.13	0.02
CKD stage (ref: transplant)			0.04
1–5	−0.02	−0.08 to 0.05	
Dialysis	−0.14	−0.25 to −0.03	
Global SES index, quartile (ref: SES quartile 4)			0.02
1 (lowest)	−0.13	−0.22 to −0.05	
2	−0.07	−0.15 to 0.01	
3	−0.05	−0.13 to 0.03	
Ethnicity (ref: Caucasian)	−0.02	−0.08 to 0.04	0.52
Time <sup>a</sup> CKD stage			0.01
Effect of time of follow-up on:			
Transplant	ref	ref	
Stages 1–5	−0.003	−0.02 to 0.02	
Dialysis	0.05	0.02 to 0.09	

CI, confidence interval; CKD, chronic kidney disease; MAU; multi-attribute utility; ref, referent; SES, socioeconomic status.

<sup>a</sup>All the CKD stages are at baseline; e.g., the interaction term of time with the dialysis cohort (time\*dialysis) refers to the baseline dialysis cohort.

### The trajectory of MAU scores over time, stratified by CKD stage

An interaction occurred between CKD stage at baseline and follow-up time ( $P = 0.01$ ), indicating that the slopes of the MAU scores differed between children with various stages of CKD at baseline. Compared to kidney transplant recipients at baseline, the change in the mean (95% CI) MAU score for children with CKD stages 1–5 at baseline was  $-0.003$  ( $-0.02$  to  $0.02$ ) per year. For children with dialysis at baseline, the mean MAU scores increased by  $0.05$  (95% CI  $0.01$  to  $0.09$ ) per year over the 4 years, or about  $0.2$  in total (Table 1 and Figure 4).

### The trajectory of SAU scores over time, stratified by CKD stage

Analysis of the SAU scores showed that the interaction between baseline CKD stage and time was significant for the attributes of pain ( $P < 0.001$ ), emotion ( $P = 0.05$ ), and dexterity ( $P = 0.03$ ), after adjusting for sex, age, ethnicity, and

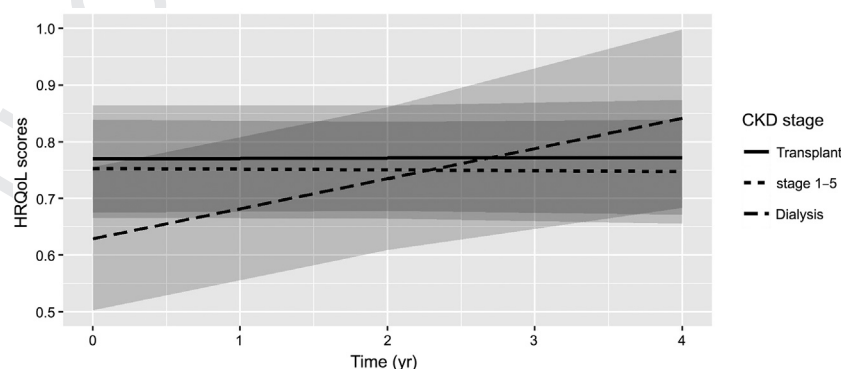
SES. No interactions occurred between baseline CKD stage and follow-up time for other attributes, including vision, hearing, speech, ambulation, and cognition. Compared to children with a functioning kidney transplant at baseline, changes in mean SAU scores in the attributes of pain, emotion, and dexterity were  $0.07$  (95% CI  $0.03$  to  $0.10$ ),  $0.03$  (95% CI  $0.005$  to  $0.05$ ) and  $0.02$  (95% CI  $0.01$  to  $0.04$ ) per year, respectively, in children treated with dialysis at baseline. For children with CKD stages 1–5, the corresponding change in mean SAU scores for pain, emotion, and dexterity were  $0.02$  (95% CI  $-0.002$  to  $0.04$ ),  $0.01$  (95% CI  $-0.004$  to  $0.02$ ), and  $0.01$  (95% CI  $-0.004$  to  $0.02$ ), respectively, compared to children with kidney transplants at baseline. The predicted changes in SAU scores for the attributes of pain, emotion, and dexterity by CKD stage are shown in Supplementary Table S4 and Supplementary Figure S2.

### Changes in health states and the effects on MAU scores over time (Supplementary Table S5)

The change in mean MAU scores between baseline and year 2 for those who changed health states to transplantation (who transitioned from dialysis to transplant and advanced CKD stage to transplant), was  $0.09$  (95% CI  $-0.05$  to  $0.23$ ; Cohen's  $d$  for effect size =  $0.31$ ). In contrast, for those whose CKD stage remained unchanged, the change in mean MAU scores was  $-0.002$ , (95% CI  $-0.04$  to  $0.03$ ; Cohen's  $d$  for effect size =  $-0.01$ ). Among children who commenced dialysis either from advanced-stage CKD or transplant, the change in mean MAU scores was  $0.02$ , (95% CI  $-0.25$  to  $0.29$ ; Cohen's  $d$  for effect size =  $0.09$ ). The data from between years 2 and 4 were insufficient to conduct a meaningful analysis of the change in HRQoL scores and effect sizes.

### DISCUSSION

In this large multicenter prospective observational study over 4 years, designed to explore the longitudinal changes in preference-based HRQoL across the full spectrum of CKD and treatment modalities, we found differential effects of time on the overall and attribute-specific HRQoL with CKD stage. The health status of most children with early- to moderate-stage CKD and with kidney transplants at study inception



**Figure 4 | Predicted multi-attribute utility (MAU) scores over 4 years of follow-up across different chronic kidney disease (CKD) stages at baseline.** The movement of MAU scores has been plotted for CKD stages at baseline. Health Utility Index score range:  $-0.36$  to  $1.0$ . HRQoL, health-related quality of life.

remained relatively unchanged, and these children had stable multi- and single-attribute utility scores as they aged. Children treated with dialysis at baseline reported significant improvements in their MAU scores, with a mean increment of 0.05 per year over the 4-year period. This change is relevant, as prior studies have indicated that differences of 0.03 or greater in the mean MAU scores are clinically important.<sup>17,23</sup> The transition from dialysis to transplant may have accounted for this improvement, noting that over 50% of children (22 of 43) who were treated with dialysis at baseline received a kidney transplant by year 4.

Longitudinal assessments of HRQoL have been performed in children in the context of chronic diseases, including cancer and asthma, with studies reporting considerable variability in utility scores over time.<sup>24,25</sup> HRQoL is a health construct that is not always constant across the illness trajectory but may vary as expectations and experiences (shaped by factors such as sex, age, SES, and disease treatment) change over time.<sup>4,26</sup> Our research findings have confirmed this dynamic nature of the HRQoL in the pediatric dialysis population. We observed improved utility scores for children on dialysis at baseline but relatively stable scores (both multi- and single-utility attributes) for the early-to-moderate CKD-stage and transplant populations over time. These are novel findings, as most studies on HRQoL in pediatric CKD populations are cross-sectional and include small samples,<sup>14,27,28</sup> with no data evaluating long-term changes in HRQoL.

Our data also showed that not all changes in CKD stages corresponded to an observed change in HRQoL. Perceptions of illnesses are subjective,<sup>29</sup> and the expectations of health outcomes may have influenced how the children and caregivers evaluated their HRQoL.<sup>30,31</sup> Some of our participants, who have experienced a lifelong impact of CKD, may not have considered experiences of poorer health as having a profound effect on their HRQoL because their expectations of health are equally low, or they may have adapted to their disease states. This possibility is reflected in our findings, as we observed relatively stable HRQoL scores in children, even those with a deterioration in their health state (such as allograft loss and the transition from transplantation back to dialysis). Conversely, children who have been in good health may have higher expectations of their future quality of life,<sup>30</sup> and a new diagnosis of kidney disease may significantly diminish these expectations.

Compared with the Longitudinal Study of Australian Children (LSAC),<sup>32</sup> we found that the primary caregivers of our study were less likely to be employed (60% compared to 75%) and belonged to a lower-income category. Such disparity was even more pronounced (58% unemployed) among the caregivers of children on dialysis.<sup>33</sup> Our data confirmed the disproportionate burden of CKD in disadvantaged communities and the high disease burden experienced by the children, which further restricted employment opportunities for the caregivers.

Children treated with dialysis also endured the highest levels of disability. Specifically, children on dialysis had poorer HRQoL scores in dexterity, emotion, and pain, in comparison

to those who had a transplant. With disease progression, children on dialysis may experience debilitating symptoms, including bone pain and fatigue, which may have overwhelming impacts on their physical functioning.<sup>34,35</sup> Children on dialysis have a sense of losing their independence, with machine dependence, a high reliance on caregivers, and a restricted lifestyle, leading to anxiety, frustration, and feelings of helplessness,<sup>36</sup> which could be associated with diminished HRQoL scores in emotion. Additionally, these children can also experience decreased gross motor function from reduced physical activity.<sup>37</sup> This decrease may have contributed to the decrements in dexterity scores. Our study findings revealed important improvements in the HRQoL scores over time in the domains of pain, emotion, and dexterity of patients who had been on dialysis at baseline. This change may, in part, be associated with the transition from dialysis to transplant. Interventions to improve not just graft survival, but also the overall well-being and life participation of children with CKD should be a priority for future research. Effective management strategies, such as early screening and interventions for bone diseases, effective pain management strategies, dietary modifications, and individualized assessment should be integral to the patient's care plan.

The strength of this study lies in the prospective, longitudinal measurement of quality-of-life outcomes. This study included 5 (of 8) pediatric nephrology centers in Australia and New Zealand and is one of the largest studies to measure multi- and single-attribute utility scores across all stages of CKD in children and adolescents over time. The HUI3 scores appeared to have reasonable known group and discriminant validity, as the responses enabled separation between children with different stages of CKD. The HUI3 instrument also has high acceptability in this population, as the level of missingness within the individual attributes was low at baseline.

The study has several potential limitations. Over 30% and 50% of the cohort at baseline did not participate in the follow-up at years 2 and 4, respectively. Their baseline characteristics are provided in [Supplementary Tables S6–S9](#). Children who were lost to follow-up were older, had earlier-stage CKD at baseline, were from lower-SES backgrounds, and were more likely to have congenital anomalies of the kidney and urinary tract (CAKUT) or glomerulonephritis as their primary cause of kidney disease. Differential dropout (data missing not at random) across CKD stages over the 4 years may have also biased the longitudinal HRQoL estimates across baseline CKD stage. The systematic attrition also may have reduced the generalizability of our findings and the statistical power to detect the effects of interest. Due to the small number of children with earlier-stage CKD, children with CKD stages 1–2 and 3–5 were combined into a single category in the analyses, ensuring power was sufficient for the longitudinal analyses.

Given the observational nature of this study, our participants may have been at different points on their disease trajectories when their HRQoL was measured. Despite multiple utility scores being measured over the course of the study, we

were unable to truly ascertain the specific points on which the child's disease trajectories and complications were assessed. Although the HUI3 instrument was able to capture a relative change in the HRQoL as our children transitioned between disease stages, the change (as measured by the effect size) was small, compared to the minimally important difference for this instrument, for transitions to a worse stage (commencement of dialysis due to disease progression or allograft loss). A disease- or condition-specific HRQoL instrument may be more responsive to a "treatment" effect than a generic HRQoL instrument. Hybrids of generic and disease-specific HRQoL instruments have been recommended by prior studies, to measure quality of life using methods that integrate patient preferences.<sup>38,39</sup> For example, Cella *et al.*<sup>40</sup> have described the functional assessment of chronic illness therapy (FACIT) approach in the context of cancer patients. Further investigation is needed into hybrid measures applicable to children with CKD.

In our study, the HRQoL measure was reported by a single person (caregiver or when possible, the child), and potential discrepancies between caregiver and child reports in responses to the HUI3 were not assessed. We also did not have information regarding the proportion of HUI3 completed by the children and the caregivers. The differences in the perceptions of HRQoL between children with CKD and their caregivers could have led to a bias in the results.<sup>6,40</sup> Furthermore, the source value set for the HUI3 instrument was derived from an adult Canadian population<sup>22</sup> and therefore may not be representative of a pediatric cohort with chronic illness. HRQoL reported by parent proxy is an established and validated practice, given the child's cognitive immaturity and dependency on their caregivers.<sup>41,42</sup> For children of very young ages, parent proxy reports are the only method of eliciting HRQoL information. Prior studies have indicated that parent proxy reports are moderately correlated with child reports, with higher agreement related to objective domains, such as physical activity, functioning, and symptoms, and poorer concordance in social and emotional domains.<sup>42–45</sup> The magnitude and direction of the differences between the child and parent proxies vary with the health conditions, valuation methods, and proxy types. A recent study conducted in Taiwan that examined the HRQoL using the Pediatric Quality of Life Inventory (PedsQL) in children with early-stage CKD found on average, lower HRQoL scores reported by parents than by children and adolescents. Similar findings were observed in Korea and the US.<sup>2,45,46</sup> In our study, the HRQoL measure was reported by a single person (caregiver, or when possible, the child), and potential discrepancies between caregiver and child in completing the HUI3 were not assessed. Future studies should incorporate the child's perspective in the assessments, ensuring that all perspectives on the HRQoL evaluation are considered.

Our findings also may not be generalizable to non-English speaking families or to low-/middle-income countries. Approximately 28% of children and families declined to participate, and selection bias may limit the conclusions that

can be drawn from the study findings. The characteristics of patients and families who did not participate, and the reasons for refusal, were not available. Therefore, we could not determine the characteristic differences between the eligible families that participated and those that did not.

## Conclusion

Children treated with dialysis had the greatest burden of disability and a lower HRQoL at baseline, but an improvement in multi- and single-attribute utility scores was observed over time. The transition from dialysis to transplantation may have contributed to the improvement in the HRQoL in children treated with dialysis at baseline. In contrast, the CKD status and HRQoL of children with CKD stages 1–5 and kidney transplants remained stable over time.

## DISCLOSURE

All the authors declared no competing interests.

## ACKNOWLEDGEMENTS

CG and GW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank all participating patients, families, and pediatric nephrology centers for their longstanding support of the study. Funding was provided by a National Health and Medical Research Council (NHMRC) BEAT-CKD program grant and the Ludwig Engel Research Fellowship. CG is supported by an NHMRC postgraduate scholarship (APP2014258). AVZ is supported by an NHMRC postgraduate scholarship (APP1115259). AH is supported by Medical Research Futures Funds (Australia) Preventive and Public Health Research (APP1199902). SP receives support as a UK National Institute for Health Research (NIHR) Senior Investigator (NF-SI-0616-202402) and from the NIHR Applied Research Collaboration (ARC) Oxford and Thames Valley. GW is supported by an NHMRC career development fellowship (APP 1147657) and investigator grant (APP1195414).

## AUTHOR CONTRIBUTIONS

CG was responsible for manuscript drafting, data interpretation, and statistical analysis, with assistance from AVZ, RK, SK, and GW. GW was the chief investigator for the study and was responsible for study conceptualization and design. ATP provided guidance with statistical analysis. All listed authors contributed to data interpretation and provided critical feedback on the article.

## SUPPLEMENTARY MATERIAL

[Supplementary File \(Word\)](#)

**Figure S1.** Directed acyclic graph.

**Figure S2.** Predicted single-attribute utility (SAU) scores (pain, emotions, dexterity) over 4 years' follow-up across different chronic kidney disease (CKD) stages at baseline.

**Table S1.** Baseline characteristics of children with chronic kidney disease (CKD) and their caregivers.

**Table S2.** Distribution of data and missingness.

**Table S3.** Cross-sectional assessment of the mean and median multi-attribute utility (MAU) scores by chronic kidney disease (CKD) stage at baseline, and at years 2 and 4.

**Table S4.** Mixed model for single-attribute utility (SAU) scores with interaction term between baseline chronic kidney disease (CKD) stage and follow-up time.



**Table S5.** Changes in health status and the corresponding change in multi-attribute utility (MAU) scores from baseline to year-2 follow-up.

**Table S6.** Characteristics of children with missing chronic kidney disease (CKD) stage versus available data in year 2; *n* (%).

**Table S7.** Characteristics of children with missing multi-attribute utility (MAU) scores versus available data in year 2; *n* (%).

**Table S8.** Characteristics of children with missing chronic kidney disease (CKD) stage versus available data in year 4; *n* (%).

**Table S9.** Characteristics of children with missing multi-attribute utility (MAU) scores versus available data in year 4; *n* (%).

## REFERENCES

- McKenna AM, Keating LE, Vigneux A, et al. Quality of life in children with chronic kidney disease—patient and caregiver assessments. *Nephrol Dial Transplant*. 2006;21:1899–1905.
- Gerson AC, Wentz A, Abraham AG, et al. Health-related quality of life of children with mild to moderate chronic kidney disease. *Pediatrics*. 2010;125:e349.
- Wong CJ, Moxey-Mims M, Jerry-Fluker J, et al. CKiD (CKD in children) prospective cohort study: a review of current findings. *Am J Kidney Dis*. 2012;60:1002–1011.
- Didsbury MS, Kim S, Medway MM, et al. Socio-economic status and quality of life in children with chronic disease: a systematic review. *J Paediatr Child Health*. 2016;52:1062–1069.
- Ploos van Amstel S, Noordzij M, Borzych-Duzalka D, et al. Mortality in children treated with maintenance peritoneal dialysis: findings from the International Pediatric Peritoneal Dialysis Network Registry. *Am J Kidney Dis*. 2021;78:380–390.
- Kiliś-Pstrusińska K, Medyńska A, Chmielewska IB, et al. Perception of health-related quality of life in children with chronic kidney disease by the patients and their caregivers: multicentre national study results. *Qual Life Res*. 2013;22:2889–2897.
- Ferris ME, Miles JA, Seamon ML. Adolescents and young adults with chronic or end-stage kidney disease. *Blood Purif*. 2016;41:205–210.
- Wells GA, Russell AS, Haraoui B, et al. Validity of quality of life measurement tools—from generic to disease-specific. *J Rheumatol*. 2011;88:2.
- Grootenhuys MA, Stam H, Last BF, Groothoff JW. The impact of delayed development on the quality of life of adults with end-stage renal disease since childhood. *Pediatr Nephrol*. 2006;21:538–544.
- Tong A, Tjaden L, Howard K, et al. Quality of life of adolescent kidney transplant recipients. *J Pediatr*. 2011;159:670–675.e672.
- Reynolds JM, Morton MJ, Garralda ME, et al. Psychosocial adjustment of adult survivors of a paediatric dialysis and transplant programme. *Arch Dis Child*. 1993;68:104–110.
- Wong G, Medway M, Didsbury M, et al. Health and wealth in children and adolescents with chronic kidney disease (K-CAD study). *BMC Public Health*. 2014;14:307.
- Francis A, Didsbury MS, van Zwieten A, et al. Quality of life of children and adolescents with chronic kidney disease: a cross-sectional study. *Arch Dis Child*. 2019;104:134–140.
- Dotis J, Pavlaki A, Printza N, et al. Quality of life in children with chronic kidney disease. *Pediatr Nephrol*. 2016;31.
- von Elm ED, Altman DGP, Egger MP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–1457.
- Bisegger C, Cloetta B, von Rueden U, et al. Health-related quality of life: gender differences in childhood and adolescence. *Soz Präventivmed*. 2005;50:281–291.
- Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. *Health Qual Life Outcomes*. 2003;1:54.
- Feeny D, Furlong W, Torrance GW, et al. Multiattribute and single-attribute utility functions for the Health Utilities Index Mark 3 System. *Med Care*. 2002;40:113–128.
- Davison SN, Jhangri GS, Feeny DH. Comparing the Health Utilities Index Mark 3 (HUI3) with the short form-36 preference-based SF-6D in chronic kidney disease. *Value Health*. 2009;12:340–345.
- Davison SN, Jhangri GS, Feeny DH. Evidence on the construct validity of the Health Utilities Index Mark 2 and Mark 3 in patients with chronic kidney disease. *Qual Life Res*. 2008;17:933–942.
- Cooper JT, Lloyd A, Sanchez JGG, et al. Health-related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. *Health Qual Life Outcomes*. 2020;18:310.
- Nakagawa S, Cuthill IC. Effect size, confidence interval and statistical significance: a practical guide for biologists. *Biol Rev*. 2007;82:591–605.
- Abel H, Kephart G, Packer TL, Warner G. Discordance in utility measurement in persons with neurological conditions: a comparison of the SF-6D and the HUI3. *Value Health*. 2017;20 8:1157–1165.
- Maurice-Stam H, Oort FJ, Last BF, et al. Longitudinal assessment of health-related quality of life in preschool children with non-CNS cancer after the end of successful treatment. *Pediatr Blood Cancer*. 2008;50:1047–1051.
- Li Z, Leite W, Thompson LA, et al. Determinants of longitudinal health-related quality-of-life change in children with asthma from low-income families: a report from the PROMIS Pediatric Asthma Study. *Clin Exp Allergy*. 2017;47:383–394.
- Cruz M, Andrade C, Urrutia M, et al. Quality of life in patients with chronic kidney disease. *Clinics (São Paulo, Brazil)*. 2011;66:991–995.
- Ruidiaz-Gómez KS, Higuera-Gutiérrez LF. Impact of chronic kidney disease on health-related quality of life in the pediatric population: meta-analysis. *J Pediatr (Rio J)*. 2021;97:478–489.
- Pardede S, Rafli A, Gunardi H. Quality of life in chronic kidney disease children using assessment Pediatric Quality of Life Inventory. *Saudi J Kidney Dis Transpl*. 2019;30:812.
- Jansen DL, Heijmans MJWM, Rijken M, et al. Illness perceptions and treatment perceptions of patients with chronic kidney disease: different phases, different perceptions? *Br J Health Psychol*. 2013;18:244–262.
- Carr AJ, Gibson B, Robinson PG. Measuring quality of life: Is quality of life determined by expectations or experience? *BMJ*. 2001;322:1240–1243.
- Tasmoc A, Hogas S, Covic A. Clinical research. A longitudinal study on illness perceptions in hemodialysis patients: changes over time. *Arch Med Sci*. 2013;9:831–836.
- Australian Bureau of Statistics. The Longitudinal Study of Australian Children. *annual report*. Available at xxxx. Accessed July 16, 2022.
- Didsbury M, van Zwieten A, Chen K, et al. The association between socioeconomic disadvantage and parent-rated health in children and adolescents with chronic kidney disease—the Kids with CKD (KCAD) study. *Pediatr Nephrol*. 2019;34:1237–1245.
- Santoro D, Satta E, Messina S, et al. Pain in end-stage renal disease: a frequent and neglected clinical problem. *Clin Nephrol*. 2013;(suppl 1): S2–S11.
- Massengill SF, Ferris M. Chronic kidney disease in children and adolescents. *Pediatr Rev*. 2014;35:16–29.
- Tjaden L, Tong A, Henning P, et al. Children's experiences of dialysis: a systematic review of qualitative studies. *Arch Dis Child*. 2012;97:395.
- Clapp EL, Bevington A, Smith AC. Exercise for children with chronic kidney disease and end-stage renal disease. *Pediatr Nephrol*. 2012;27:165–172.
- Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care*. 1989;27:S217–S232.
- Casali P, Licitra L, Constantini M, et al. Quality of life assessment and clinical decision-making. *Ann Oncol*. 1997;8:1207–1211.
- Cella D, Nowinski CJ. Measuring quality of life in chronic illness: the functional assessment of chronic illness therapy measurement system. *Arch Phys Med Rehabil*. 2002;83(12 suppl 2):S10–S17.
- Eiser C, Mohay H, Morse R. The measurement of quality of life in young children. *Child: Care, Health Develop*. 2000;26:401–414.
- Kerklaan J, Hannan E, Baumgart A, et al. Patient- and parent proxy-reported outcome measures for life participation in children with chronic kidney disease: a systematic review. *Nephrol Dial Transplant*. 2020;35:1924–1937.
- Davis E, Nicolas C, Waters E, et al. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. *Qual Life Res*. 2007;16:863–871.
- Jiang M, Ma Y, Li M, et al. A comparison of self-reported and proxy-reported health utilities in children: a systematic review and meta-analysis. *Health Qual Life Outcomes*. 2021;19:45.
- Tain YL, Lu PC, Kuo HC, Hsu CN. Differences in health-related quality of life in children with chronic kidney disease as reported by children and parent proxies. *Pediatr Nephrol*. 2022. <https://doi.org/10.1007/s00467-022-05621-2>. Published online June 9.
- Baek HS, Kang HG, Choi HJ, et al. Health-related quality of life of children with pre-dialysis chronic kidney disease. *Pediatr Nephrol*. 2017;32:2097–2105.