Predictors of Long-Term Health-Related Quality of Life in Adolescent Solid Organ Transplant Recipients

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Objectives This study aimed to identify prospective predictors of health-related quality of life (HRQOL) for adolescent solid organ (kidney, liver, heart, lung) transplant recipients. **Methods** Data regarding demographics, individual/transplant characteristics, and environmental characteristics were gathered from 66 adolescent transplant recipients and their families at baseline and used to predict the physical functioning, mental health, and general health perceptions domains of HRQOL 18 months later. **Results** Baseline levels of HRQOL explained the greatest amount of variance in levels of HRQOL at follow-up; however, specific demographic (i.e., income), individual/transplant (i.e., adherence, frequency of rescheduled clinic appointments, and presence of a rejection episode), and environmental factors (i.e., family conflict) contributed to the variance in HRQOL domains beyond baseline levels. **Conclusions** This study identified certain modifiable individual and environmental factors and non-modifiable risk factors associated with lower future HRQOL. Transplant centers should begin screening and addressing these factors to potentially improve HRQOL.

Key words adolescents; health-related quality of life; pediatric transplantation.

Introduction

With increased survival rates for pediatric transplant recipients, there has been greater attention to children's and adolescents' health-related quality of life (HRQOL) following transplantation (Anthony, BarZiv, & Ng, 2010). HRQOL is a multidimensional construct including, but not limited to, an individual's physical and mental health, and psychosocial well-being (De Civita et al., 2005). Assessing HRQOL is important to understand the impact of illness and transplantation on daily functioning and well-being. Further, HRQOL is often used to evaluate the effectiveness of interventions and to guide clinical decision-making (Modi & Quittner, 2003). Investigations of HRQOL in adolescent transplant recipients are particularly important given the unique developmental needs and tasks associated with adolescence, which differentiates them from adults and children (for a review of relevant issues for adolescent transplant recipients, see Kaufman, Shemesh, & Benton, 2010). Additionally, poor HRQOL has been shown to be associated with important medical outcomes including more frequent hospitalizations in pediatric transplant recipients (Bucuvalas et al., 2003) and higher rates of anxiety and depression in youth with chronic illness (Cruz, Marciel, Quittner, & Schechter, 2009; Hassan, Loar, Anderson, & Heptulla, 2006).

As research on HRQOL for pediatric transplant recipients has developed, studies have begun to identify pre- and posttransplant factors associated with HRQOL

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(Anthony et al., 2010). Elucidating factors that influence future HRQOL is the next important step in informing the development of interventions to improve HRQOL for pediatric transplant recipients. Despite the importance of this work, the majority of research in this area has utilized a cross-sectional design, therefore limiting inferences that can be made regarding the directionality of effects (Alonso et al., 2008, 2010; Fredericks, Lopez, Magee, Shieck, & Opipari-Arrigan, 2007; Sundaram, Landgraf, Neighbors, Cohn, & Alonso, 2007). The aim of the current study was to prospectively examine predictors of HRQOL 18 months after an initial assessment in a sample of adolescents who have received a solid organ (i.e., kidney, liver, heart, and lung) transplant.

To identify potential predictors and aid in the interpretation of results, the revised model of HRQOL by Wilson and Cleary (1995) was utilized as a guiding theoretical construct (Ferrans, Zerwic, Wilbur, & Larson, 2005). The overarching tenet behind this model is that HRQOL is multidimensional, subjective, and determined by characteristics of both the individual and the environment. For the current study, we examined the predictive utility of demographic, individual, and environmental characteristics on three specific domains of HRQOL—physical functioning, mental health, and general health perceptions. Physical functioning involves one's perceived energy level and ability to participate in one's environment and daily activities; mental health involves one's perceived emotional and psychological well-being; and general health perceptions involve one's perceived overall health. Physical functioning and mental health were chosen because they are commonly included in measurements of HRQOL, are frequently examined as HRQOL outcomes, and capture large portions of adolescents' daily experiences following transplantation (Anthony et al., 2010). The domain of general health perceptions was chosen because it is included in Wilson and Cleary's model, has been examined in other studies with adolescent transplant recipients (Fredericks et al., 2008), and is linked to important health outcomes, such as health care utilization (Hollifield, Paine, Tuttle, & Kellner, 1999). With regard to predictors, although demographic factors were considered a subset of individual characteristics in the Wilson and Cleary model, demographic factors were examined separately in this study. Isolating demographic factors allowed for identification of potentially modifiable individual variables that could contribute to HRQOL beyond basic demographic information (see Figure 1 for an overview of the factors examined in this study).

Studies examining the association between demographic factors and HRQOL have produced inconsistent results. For example, Caucasian race was associated with higher parent-reported physical HRQOL (Bucuvalas et al., 2003) and lower parent-reported mental health HRQOL (cross-sectional investigation using a subsample of the current sample; Simons et al., 2008), but was unrelated to HRQOL in other studies (Fredericks et al., 2008; Sundaram et al., 2007). However, gender has consistently been found to be unrelated to HRQOL (Bucuvalas et al., 2003; Cole et al., 2004; Fredericks et al., 2007; Sundaram et al., 2007). Associations among socio-economic factors and HRQOL have not been widely examined, but one

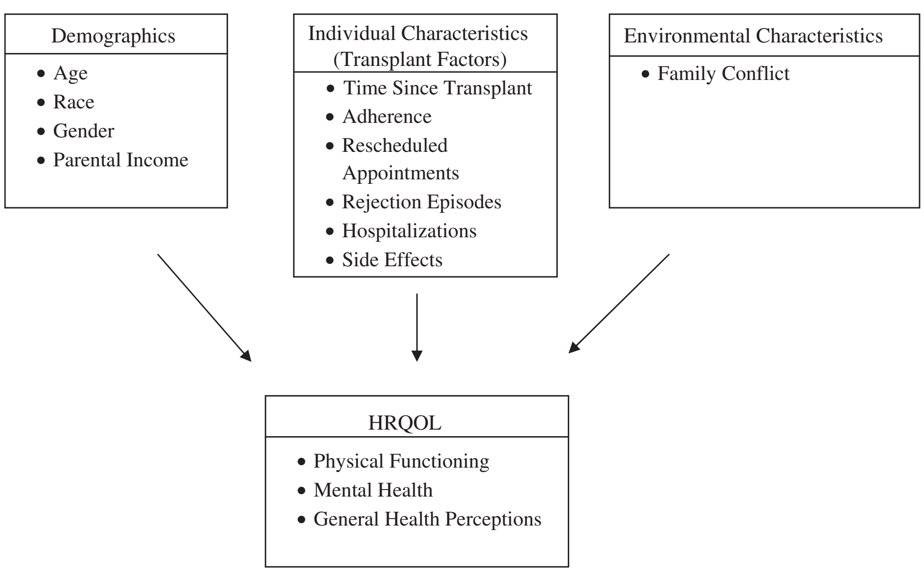

Figure 1. Factors influencing HRQOL based on Wilson and Cleary's (1995) model.

study reported that maternal education, often used as a proxy for socio-economic status (SES), was associated with higher psychosocial HRQOL scores (Bucuvalas et al., 2003).

Individual characteristics have been described by Ferrans and colleagues (Ferrans et al., 2005) to include ''developmental, psychological, and biological factors that influence health outcomes'' (p. 337). In the current study, we focused on transplant-related factors. Although some individual characteristics may not be modifiable, such as age at transplantation or years since transplantation, others may be, such as rate of clinic attendance and, potentially, hospitalizations and rejection episodes (e.g., Bucuvalas et al., 2003; Fredericks et al., 2008). Unfortunately, not all of these factors (e.g., rejection episodes) have been well examined and studies investigating these factors have not yielded consistent results. For example, one study found that younger age at transplantation was associated with greater HRQOL and that time since transplant was inversely correlated with HRQOL (Bucuvalas et al., 2003). However, these findings were not replicated (Alonso et al., 2003; Fredericks et al., 2007). Hospitalizations were predictive of poorer physical HRQOL in one study (Bucuvalas et al., 2003), but not in others (Alonso et al., 2003; Sundaram et al., 2007). Additionally, nonadherence to clinic appointments was associated with poorer HRQOL in one study of children and adolescents (Fredericks et al., 2007) but not another (Fredericks et al., 2008).

Special attention must be paid to adherence to medical regimens, as rates of nonadherence tend to be higher for adolescents compared to other age groups and nonadherence is a significant risk factor for poor outcomes (Kaufman et al., 2010; Rianthavorn & Ettenger, 2005). For example, nonadherence has been linked to adolescent social limitations due to emotional/behavioral difficulties, as reported by parents (Fredericks et al., 2007). Nonadherence, as determined by standard deviation of trough tacrolimus blood levels, was also predictive of poorer HRQOL in adolescents (Fredericks et al., 2008). Further, in previous cross-sectional analyses with this sample, perceived frequency of medication side effects, often considered a barrier to adherence, was associated with poorer physical and mental health HRQOL for pediatric transplant recipients (Simons et al., 2008).

Environmental characteristics have been categorized as social or physical, including influences such as family relationships and neighborhood characteristics (Ferrans et al., 2005). For adolescent transplant recipients, families usually have high levels of involvement in healthcare management. Adolescent HRQOL has been found to be negatively associated with general family conflict (Simons et al., 2008; Taylor, Franck, Gibson, Donaldson, & Dhawan, 2009).

Although prior research has identified associations among demographics, individual characteristics, environmental factors, and HRQOL, there are very little prospective data examining the predictive utility of individual and environmental characteristics on future HRQOL. Therefore, the present study aimed to identify prospective predictors of HRQOL over 18 months in a sample of adolescent solid organ transplant recipients. Although long-term HRQOL appears to be relatively stable over time (Devine, Reed-Knight, Simons, Mee, & Blount, 2010), identification of factors predictive of future HRQOL is important for informing intervention research. We hypothesized that specific individual (transplant-related) and environmental factors would predict HRQOL at Time 2 beyond baseline levels of HRQOL among pediatric transplant recipients. Based on Wilson and Cleary's (1995) model, we expected that more medication side effects, the presence of a rejection episode, the presence of a hospitalization, greater number of rescheduled clinic appointments, poorer medication adherence, and greater levels of general family conflict would be significant predictors of lower physical functioning, mental health, and general health perceptions at 18-month follow-up. We did not have specific hypotheses regarding demographic variables as previous findings have been inconsistent.

Methods

Participants

This investigation included 18-month longitudinal data collected on two occasions from a sample of adolescents who had received a solid organ transplant (kidney, liver, heart, and lung) at a single medical institution. The initial sample at Time 1 included 82 adolescent patients between the ages of 11 and 20 years ($M = 15.8$, $SD = 2.4$) who received solid organ transplants (47 kidney, 20 liver, 14 heart, and 1 double lung). Adolescents and/or parents were eligible to participate. Eighty parents and 71 adolescents participated in the study, representing a total of 82 patients and including 68 parent–adolescent dyads. Fifty-six percent of adolescents were male and adolescents were Caucasian (61%), African American (32%), and other races (7%). Additional demographic information is detailed in table format in the study by Simons & Blount (2007). Time since first transplant at Time 1 ranged from 4 months to 16.5 years ($M = 5.66$ years, $SD = 4.85$ years, median = 3.79 years). Inclusion criteria for participation at Time 1 were that the adolescent was at least 11 years old, lived with at least one parent, was English speaking, and had received a solid organ transplant at least 4 months prior to participation. Only parents completed measures when they reported that their adolescent was developmentally delayed ($n = 7$ or 9% of original sample).

The follow-up sample at Time 2 included 66 adolescent and young adult transplant patients from the original sample (39 kidney, 16 liver, 10 heart, and 1 double lung). Of the 16 families who did not participate at Time 2, seven families could not be contacted after repeated attempts, five patients died before re-enrollment, two families could not be contacted due to disconnected phones, and two families were no longer followed at the medical institution, resulting in an 87% retention rate for eligible families. Again, adolescents and/or parents could participate. The Time 2 sample consisted of 63 parents and 51 adolescent/young adult participants, representing a total of 66 patients, with 49 parent-adolescent dyads. Participants were between the ages of 12 and 22 years ($M = 17.1$, $SD = 2.4$), and were predominantly male (55%) and Caucasian (62%), with the remainder of the sample being African American (29%), and other races (9%). Similar to initial interviews, only parents were interviewed for developmentally delayed adolescents ($n = 5$ or 8% of sample). There were no significant differences on demographic or medical factors (time since transplant, days hospitalized, rescheduled clinic appointments, presence of rejection episode) between follow-up participant families ($n = 66$) and those who did not participate ($n = 16$). Additionally, there were no differences in Time 1 levels of HRQOL between participants at Time 2 and nonresponders. For the 66 families who participated, the time lapse between initial and follow-up interviews ranged from 12 to 20 months ($M = 16.5$, $SD = 1.5$). Time since transplant at Time 2 ranged from 1.5 to 18.0 years ($M = 7.34$, $SD = 5.11$, median = 5.29 years).

Procedures

Following institutional review board approval, adolescents and parents from the original study were invited to participate at Time 2. Patients and parents were contacted during clinic appointments or via telephone. New informed consent, assent, and HIPAA release forms were obtained at clinic or via postal mail after initial contact was made with the family. The structured interview with each parent and adolescent consisted of verbal administration of all study measures over the phone. Trained research assistants conducted the structured interviews. Parent interview length ranged from 35 to 112 min ($M = 58.6$, $SD = 15.8$) and adolescent interview length ranged from 25 to 60 min ($M = 37.2$, $SD = 7.4$). Twenty dollar gift cards were provided for participation.

Measures

Demographic Information

Demographic information collected about the adolescent included: (a) age, (b) gender, and (c) race. Race was dichotomized as Caucasian or Other (coded as 1 or 0, respectively) for all analyses given that 91% of the sample was either Caucasian or African American. Demographic information collected about the parent included: (a) marital status, (b) educational attainment, and (c) income.

HRQOL

Adolescent Self-report. The Child Health Questionnaire-Child Form 87 (CHQ-CF87; Landgraf, Abetz, & Ware, 1999) is an 87-item generic measure of HRQOL for adolescents 12–18 years of age. Although 10 of our participants were outside of this age range at Time 2, we utilized the measure for consistency with Time 1. Although other measures of HRQOL were available, the CHQ was chosen for its comprehensive assessment of HRQOL, the availability of adolescent and parent report forms, and because no condition-specific measures were available for transplant recipients at the initiation of the study. The CHQ is a well-established measure of HRQOL, with strong evidence of validity and reliability (Palermo et al., 2008). Each item consists of five response choices using a Likert-like rating scale and higher scores on the CHQ indicate better HRQOL. Although the CHQ-CF87 yields 12 domains, the current study examined three domains of HRQOL: physical functioning, mental health, and general health perceptions. In the present sample, alpha coefficients were .88 and .58 for Time 1 and Time 2 physical functioning, .87 and .85 for Time 1 and Time 2 mental health, and .70 and .72 for Time 1 and Time 2 general health perceptions, respectively.

Parent Report of Adolescent's Quality of Life. The Child Health Questionnaire-Parent Form 50 (CHQ-PF50; Landgraf et al., 1999) is a well-validated 50-item generic HRQOL measure for children aged 5–18 years. Again, 10 of our participants were outside of this age range at Time 2, but we utilized the measure to allow for consistency with Time 1 data. Further, although the CHQ-PF50 yields 14 domains, the three subscales corresponding to adolescent report were chosen for these analyses: physical functioning, mental health, and general health perceptions. Higher scores indicate better functioning. Extensive psychometric data exist for the CHQ-PF50 and it is used frequently in pediatric populations, including adolescent transplant recipients (Fredericks et al., 2007, 2008; Sundaram et al., 2007). In the present sample, α-coefficients were .85

and .88 for Time 1 and Time 2 physical functioning, .71 and .74 for Time 1 and Time 2 mental health, and .57 and .58 for Time 1 and Time 2 general health perceptions, respectively.

Family Conflict

The conflict subscale from the Family Environment Scale (FES; Moos & Moos, 1994) was used to assess general levels of family conflict at Time 1. Higher scores indicate higher perceived family conflict. Good internal consistency has been reported for this subscale (Moos & Moos, 1994). In our sample, Cronbach alphas for the conflict subscales were adequate ($\alpha = .61$ for adolescents and .66 for parents).

Adherence

The Medication and Clinic Attendance Modules of the Medication Adherence Measure, or MAM (Zelikovsky & Schast, 2008), were used to assess adherence to medical regimens and clinic attendance at Time 1. Using structured interviews, parents and adolescents independently reported how many doses of each medication the adolescent missed or took late in the prior 7 days. Parents and adolescents also reported on how frequently they rescheduled clinic appointments. Percent adherence was determined as the number of doses taken on-time (vs. late or missed) divided by number prescribed, times 100. Thus, higher scores indicate better adherence. Research data on the MAM suggest adequate convergent validity with established measures of adherence (Zelikovsky & Schast, 2008).

Perceived Side Effects

The End-Stage Renal Disease Symptom Checklist-Transplant Module (ESRD-SCL; Franke et al., 1999), validated for use with adult transplant patients, was adapted for use with this sample since no measure of immunosuppressant medication side effects was available for use with adolescents. The adapted scale measured the frequency of 39 different side effects (e.g., weight gain, bruising) on a 5-point Likert scale and yielded a total frequency score. Higher scores indicate more frequent perceived side effects. This measure was completed by adolescents and parents at Time 1. Adequate construct validity and internal consistency have been demonstrated for the ESRD-SCL. Cronbach alpha coefficients for frequency of side-effects were excellent at .92 for adolescent report and .87 for parent report.

Clinical Outcomes

Parents reported on: (a) transplant type, (b) date of transplant(s), (c) presence of one or more hospitalizations within the 6 months prior to the Time 1 interview, and (d) presence of one or more rejection episodes within the 6 months prior to the Time 1 interview.

Data Analyses

This study aimed to evaluate the utility of prospective predictor variables in explaining the variance in Time 2 HRQOL domains of physical, mental health, and general health perceptions. As shown in Figure 1, relevant predictor variables were identified using Wilson and Cleary's (1995) model of HRQOL and the adaptations to the model noted by Ferrans et al. (2005). Demographic and individual (transplant-related) characteristics were examined separately to determine the contribution of potentially modifiable transplant-related characteristics beyond basic, nonmodifiable demographics (i.e., age, gender, and race). Given the relatively large number of potential predictors identified by the model, preliminary analyses examined correlations between predictors and HRQOL domains to empirically determine which variables would be the most appropriate for inclusion in regression analyses. Only variables that were significantly ($p < .05$) related to HRQOL were included in regression analyses. Hierarchical regression analyses were conducted for each domain (i.e., physical functioning, mental health, general health perceptions) for each reporter (i.e., adolescent and parent), resulting in a total of six regression analyses. Due to the number of regression analyses, significance level for regression equations was set at $p < .01$ to reduce possible Type I error. Variables were entered at the following steps: (a) Time 1 level of the HRQOL domain; (b) Time 1 demographics; (c) Time 1 individual (transplant) characteristics; and (d) Time 1 environmental characteristics. Non-significant predictors were trimmed at each step to create final models.

Results

Preliminary Analyses

Two-tailed Pearson correlations were calculated between all predictors (Figure 1) and each outcome variable. Predictors that were not significantly correlated with the outcome were not entered into the regression model for that outcome. For example, time since transplantation was not significantly correlated with any of the HRQOL domains and therefore was not included in any of the regression analyses. For information regarding correlations and mean differences between parent and adolescent reports of HRQOL within dyads, please see Devine et al. (2010). Descriptive statistics for predictor and outcome variables are available in a Supplementary Table (see Supplementary Digital Content 1).

Physical HRQOL

The following variables were significantly correlated with Time 2 adolescent-reported physical HRQOL: (a) demographics: age ($r = .30$, $p < .05$), race ($r = .28$, $p < .05$), income ($r = .33$, $p < .05$); and (b) individual characteristics: adolescent-reported frequency of side effects ($r = -.37$, $p < .01$), and parent-reported rescheduled clinic visits ($r = -.30$, $p < .05$). The following variables were significantly correlated with Time 2 parent-reported physical HRQOL: (a) individual characteristics: presence of rejection episode(s) in last 6 months ($r = -.41$, $p < .01$) and adolescent-reported rescheduled clinic visits ($r = -.31$, $p < .05$).

Mental Health

The following variables were significantly correlated with Time 2 adolescent-reported mental health: (a) demographics: age ($r = -.29$, $p < .05$); (b) individual characteristics: adolescent-reported frequency of side effects ($r = -.43$, $p < .01$), parent-reported frequency of side effects ($r = -.33$, $p < .05$), and parent-reported adherence ($r = .31$, $p < .05$); and (c) environmental characteristics: adolescent-reported family conflict ($r = -.29$, $p < .05$). The following variables were significantly correlated with Time 2 parent-reported mental health: (a) individual characteristics: parent-reported adherence ($r = .30$, $p < .05$) and parent-reported frequency of side effects ($r = -.30$, $p < .05$); and (b) environmental characteristics: adolescent-reported family conflict ($r = -.44$, $p < .01$).

General Health Perceptions

The following variables were significantly correlated with Time 2 adolescent-reported general health perceptions: (a) demographics: age ($r = -.30$, $p < .05$); (b) individual characteristics: adolescent-reported frequency of side effects ($r = -.39$, $p < .01$), parent-reported frequency of side effects ($r = -.29$, $p < .05$), adolescent-reported adherence ($r = .30$, $p < .05$), presence of rejection episode(s) in the last 6 months ($r = -.44$, $p < .01$), and adolescent-reported rescheduled clinic visits ($r = .43$, $p < .01$); and (c) environmental characteristics: adolescent-reported family conflict ($r = -.27$, $p = .05$). The following variables were significantly correlated with Time 2 parent-reported general health perceptions: (a) demographics: parental income ($r = -.33$, $p < .01$); and (b) individual characteristics: presence of rejection episode(s) in the last 6 months ($r = -.25$, $p < .05$), parent-reported rescheduled clinic visits ($r = -.30$, $p < .05$), and parent-reported frequency of side effects ($r = -.32$, $p < .05$).

Although there were no differences in HRQOL related to type of transplant (i.e., kidney, liver, and heart) at Time 1 (Simons et al., 2008), we ran one-way ANOVAs to examine differences in Time 2 HRQOL by organ type for each reporter. For adolescent report, there were no differences in physical functioning or general health perceptions by organ type, $F(2, 47) = 0.18$, $p > .05$, and $F(2, 47) = 2.96$, $p > .05$, respectively. For the mental health domain, the Welch test was used due to violation of the homogeneity of variance assumption. There was a significant difference in mental health functioning by organ type, $F(2,\ 21.11) = 5.41$, $p = .013$, with heart transplant recipients reporting higher mental health functioning compared to liver transplant recipients. For parent report, there were no differences by type of transplant for physical functioning, $F(2, 60) = 1.14$, $p > .05$, mental health, $F(2, 60) = 1.14$, $p > .05$, or general health perceptions, $F(2,\ 60) = 1.14$, $p > .05$. Therefore, as we did in our previous studies (Simons et al., 2008; Devine et al., 2010), participants were collapsed across organ group for analyses, but organ type was included as a predictor in analyses with adolescent-reported mental health.

Time 1 Predictors of HRQOL 18-months Later

Physical Functioning

For adolescent-reported physical functioning, Time 1 levels of physical functioning were entered first to control for baseline levels, followed by demographics at the second step (age, race, and parental income), and individual characteristics at the third step (adolescent-reported side effects and parent-reported frequency of rescheduled clinic visits). Nonsignificant predictors were trimmed at each step, resulting in the final model shown in Table I. Parental income explained 10% of the variance above baseline levels of physical functioning and parent-reported frequency of rescheduled clinic appointments explained an additional 8%, with higher levels of parental income and lower frequency of rescheduled clinic appointments predicting higher levels of physical functioning. The final model accounted for 36% of variance in adolescent-reported physical functioning at Time 2, $R^2 = .36$, adjusted $R^2 = .32$, $F(3,\ 44) = 8.38$, $p < .001$. For parent-reported physical functioning, Time 1 physical functioning was entered first, followed by individual characteristics (presence of rejection episode in last 6 months and adolescent-reported frequency of rescheduled clinic visits). After nonsignificant effects were trimmed, only baseline levels of physical functioning remained as a predictor, accounting for 26% of the variance in Time 2 parent-reported physical functioning, $R^2 = .26$, Adjusted $R^2 = .25$, $F(1, 61) = 21.80$, $p < .001$ (Table I).

Table I. *Hierarchical Regression Time 1 Predictors of Time 2 Physical Functioning*

Variable	*B*	*SE B*	β	ΔR^2
Adolescent report ($n = 48$)				
Step 1: Control for Time 1				.18**
Time 1 physical functioning	0.35	0.11	.43**	
Step 2: Demographics				.10*
Time 1 physical functioning	0.36	0.10	.43**	
Parental income	1.57	0.63	.32*	
Step 3: Individual characteristics				.08*
Time 1 physical functioning	0.34	0.10	.41**	
Parental income	1.63	0.60	.33**	
Frequency of rescheduled clinic appointments (parent-reported)	−1.80	0.76	−.29*	
Parent report ($n = 63$)				
Step 1: Control for Time 1				.26**
Time 1 physical functioning	.68	.15	.51**	

Note. Final model for adolescent report: $R^2 = .36$, $F(3, 44) = 8.38$, $p < .001$; final model for parent report: $R^2 = .26$, $F(1, 61) = 21.80$, $p < .001$.
*$p < .05$, **$p < .01$.

Table II. *Hierarchical Regression Time 1 Predictors of Time 2 Mental Health*

Variable	*B*	*SE B*	β	ΔR^2
Adolescent report ($n = 51$)				
Step 1: Control for Time 1				.35**
Time 1 mental health	0.63	0.12	.60**	
Parent report ($n = 52$)				
Step 1: Control for Time 1				.26**
Time 1 mental health	0.55	0.13	.51**	
Step 2: Individual characteristics				.07*
Time 1 mental health	0.53	0.12	.49**	
Adherence (parent-reported)	0.38	0.17	.27*	
Step 3: Environmental characteristics				.08*
Time 1 mental health	0.45	0.12	.42**	
Adherence (parent-reported)	0.34	0.16	.24*	
Family conflict (adolescent-reported)	−2.46	0.96	−.30*	

Note. Final model for adolescent report: $R^2 = .35$, $F(1, 49) = 26.86$, $p < .001$; final model for parent report: $R^2 = .41$, $F(3, 48) = 11.35$, $p < .001$.
*$p < .05$, **$p < .01$.

Mental Health

For adolescent-reported mental health, adolescent-reported Time 1 mental health and type of transplant was entered at Step 1, followed by demographics (age) at Step 2, individual characteristics (adolescent-reported side effects, parent-reported side effects) at Step 3, and environmental characteristics (adolescent-reported conflict) at Step 4. After trimming nonsignificant effects, only baseline levels of mental health remained as a predictor, explaining 35% of the variance in Time 2 adolescent-reported mental health, $R^2 = .35$, adjusted $R^2 = .34$, $F(1, 49) = 26.86$, $p < .001$ (Table II). For parent-reported mental health, Time 1 mental health was entered at step 1, followed by individual characteristics (parent-reported frequency of side effects and parent-reported adherence) at Step 2 and environmental characteristics (adolescent-reported family conflict) at Step 3. As shown in Table II, parent-reported adherence contributed 7% of variance above baseline levels of mental health and adolescent-reported family conflict contributed an additional 8%, with higher levels of adherence and lower levels of conflict predicting better mental health HRQOL. The final model accounted for 41% of variance in parent-reported mental health at Time 2, $R^2 = .41$, adjusted $R^2 = .38$, $F(3, 48) = 11.21$, $p < .001$.

General Health Perceptions

For adolescent-reported general health perceptions, Time 1 general health perceptions was entered first, followed by demographics (age) at Step 2, individual characteristics [adolescent-reported frequency of side effects, parent-reported frequency of side effects, presence of rejection episode(s) in the last 6 months, and adolescent-reported frequency of rescheduled clinic appointments] at Step 3, and environmental characteristics (adolescent-reported family conflict) at Step 4. As shown in Table III, adolescent-reported frequency of clinic visits contributed 13% of variance above baseline levels of general health perceptions and adolescent-reported family conflict contributed an additional 5%, with higher adolescent-reported frequency of rescheduled clinic appointments and lower adolescent-reported family conflict significantly predicting higher levels of general health perceptions. The final model accounted for 63% of the variance in Time 2 general health perceptions, $R^2 = .63$, adjusted $R^2 = .60$, $F(3, 37) = 20.72$, $p < .001$. For parent-reported general health perceptions, Time 1 general health perceptions were entered at Step 1, followed by demographics (parental income) at Step 2, and individual characteristics (presence of rejection episode(s) in past 6 months, parent-reported frequency of side effects, and parent-reported frequency of rescheduled clinic appointments) at Step 3. As shown in Table III, family income contributed 5% of variance above baseline levels of general health perceptions and presence of a rejection episode contributed an additional 5%, with lower levels of parental income and the lack of a rejection episode predicting better general health perceptions. This model accounted for 61% of the variance in Time 2 parent-reported general health perceptions, $R^2 = .61$, adjusted $R^2 = .59$, $F(3, 58) = 29.78$, $p < .001$.

Table III. *Hierarchical Regression Time 1 Predictors of Time 2 General Health Perceptions*

Variable	*B*	*SE B*	β	ΔR^2
Adolescent report ($n = 41$)				
Step 1: Control for Time 1				.45**
Time 1 general health perceptions	0.76	0.13	.67**	
Step 2: Individual characteristics				.13**
Time 1 general health perceptions	0.72	0.12	.63**	
Frequency of rescheduled clinic appointments (adolescent-reported)	6.21	1.83	.36**	
Step 3: Environmental characteristics				.05*
Time 1 general health perceptions	0.70	0.11	.62**	
Frequency of rescheduled clinic appointments (adolescent-reported)	5.99	1.74	.35**	
Family conflict (adolescent-reported)	−1.71	0.78	−.22*	
Parent report ($n = 62$)				
Step 1: Control for Time 1				.51**
Time 1 general health perceptions	0.76	0.10	.71**	
Step 2: Demographics				.05*
Time 1 general health perceptions	0.72	0.09	.68**	
Parental income	−1.90	0.74	−.22*	
Step 3: Individual characteristics				.05*
Time 1 general health perceptions	0.70	0.09	.65**	
Parental income	−2.22	0.72	−.26**	
Presence of rejection episode	−8.70	3.31	−.22*	

Note. Final model for adolescent report: $R^2 = .63$, $F(3, 37) = 20.72$, $p < .001$; final model for parent report: $R^2 = .61$, $F(3, 58) = 29.78$, $p < .001$.
*$p < .05$, **$p < .01$.

Discussion

The present study examined prospective predictors of three important HRQOL domains for adolescent transplant recipients—physical functioning, mental health, and general health perceptions. Results indicated that, overall, the best predictor of future HRQOL was baseline levels of functioning for each domain. However, several demographic, individual (transplant-related), and environmental characteristics were significant predictors of Time 2 HRQOL after controlling for baseline levels. Thus, risk factors beyond initial levels of HRQOL for poor future functioning were identified. These results provide preliminary support for the use of Wilson and Cleary's (1995) model of HRQOL for adolescent transplant recipients and provide guidance for the development of clinical interventions to improve future HRQOL.

The individual characteristics that significantly predicted Time 2 HRQOL were predominantly related to adherence behaviors (i.e., rescheduled clinic appointments, self- or parent-reported medication adherence). Nonadherence to medication regimens has been related to negative physical outcomes, such as graft rejection and loss (Rianthavorn & Ettenger, 2005), as well as the HRQOL domains of mental and general health perceptions in a cross-sectional study of adolescent liver transplant recipients (Fredericks et al., 2008). Since our prospective study found adherence to predict later mental health, but not general health perceptions, future research is needed to examine the directionality of the relationship between adherence and general health perceptions since it may be that negative general health perceptions serve as a risk factor for future non-adherence. A recent study of medication adherence in adolescents with inflammatory bowel disease found that adolescents' perceived disease severity was inversely associated with adherence, whereas parents' perceptions of greater disease severity was associated with better adherence (Reed-Knight, Lewis, & Blount, 2010). More research is needed to further elucidate the relationship between adherence and health perceptions.

Clinic attendance, which is one aspect of regimen adherence, has been found to be related to HRQOL for children but not adolescents (Fredericks et al., 2007, 2008). The measure used in the current study examined the frequency of clinic appointment rescheduling, rather than attendance. This measure may identify a different group of people than are traditionally identified to transplant coordinators—individuals who are not outright failing to show for appointments, but who require frequent rescheduling or postponing of visits. Further, this measure may capture different aspects of adherence, reflecting both motivational and organizational components. The assumption is that keeping a set appointment indicates higher levels of motivation and better organization (i.e., planning, coordinating parent and child schedules, obtaining transportation, and attending an appointment). In this study, more frequently rescheduled appointments were related to poorer future physical functioning but higher future general health perceptions. Although this may seem contradictory, it may indicate that adolescents and parents who frequently reschedule clinic appointments have a sense that the adolescent's health is stable and clinic attendance is not a priority. On the other hand, it may indicate that adolescents and parents who keep appointments are more concerned with the adolescent's health, similar to past research on poorer health perceptions and greater health care utilization (Hollified et al., 1999; Reed-Knight et al., 2010). Whether rescheduling clinic visits reflects greater barriers to attending appointments or the perception that attendance is not critical, irregular appointment keeping due to a high frequency of rescheduling could translate into poorer physical functioning. Inquiring directly about the reasons for rescheduling could shed light on the barriers faced by individual families and may direct interventions to increase regular attendance at clinic appointments.

Family conflict, the environmental factor considered in this study, was a significant predictor for Time 2 parent-reported mental health and adolescent-reported general health perceptions. Family conflict has also been related to poorer adherence (DiMatteo, 2004), which in turn has been related to poorer mental health and general health perceptions (Fredericks et al., 2008). The body of research showing an association between higher rates of conflict and poorer outcomes suggests that family conflict is a key target for future interventions aimed to improve HRQOL and adherence in pediatric transplant recipients.

With regard to demographic factors, parental income was the only factor that significantly predicted Time 2 HRQOL, despite other factors correlating with Time 2 outcomes. Interestingly, lower income was associated with lower physical functioning but higher general health perceptions. The positive correlation between income and physical functioning was not surprising, as studies with adults have found poorer clinical outcomes for low SES groups (e.g., Butkus, Mayedrech, & Raju, 1992). Low SES has also been related to poorer adherence, which, in turn, has been related to graft rejection and loss (Rianthavorn & Ettenger, 2005) and lower HRQOL (Fredericks et al., 2008). Although unexpected, the fact that income was inversely associated with general health perceptions while also being positively associated with physical functioning raises interesting hypotheses for future research. Perhaps individuals from lower SES backgrounds have lower expectations for their health given that they perceive their physical functioning to be poorer, making it easier to exceed such expectations and resulting in higher general health perceptions despite lower physical functioning. Conversely, individuals from higher SES backgrounds may have unrealistically high expectations for their health, despite having good function (e.g., walking without tiring, climbing stairs, bathing unassisted).

Taken together, the results suggest that significant predictors of future HRQOL beyond baseline levels of the domain are generally behavioral indicators of adherence and family conflict, with one clinical outcome, the presence of a rejection episode, predicting parental general health perceptions. Thus, future HRQOL is influenced by individual and environmental characteristics beyond medical events. It is possible that certain medical issues, like rejection episodes, hospitalizations, and side effects are more salient in the short-term and may vary over time, thus yielding little predictive power for HRQOL 18 months later. However, behavioral characteristics, such as adherence, rescheduling of clinic appointments, and family conflict may be less likely to improve without intervention and have long-lasting impacts that enhance their predictive utility. Interestingly, hospitalizations and time since transplant at Time 1 were not correlated with Time 2 HRQOL. These transplant variables have been inconsistently related to HRQOL in other studies (Alonso et al., 2003; Bucuvalas et al., 2003; Fredericks et al., 2007). Thus, while medical issues are likely to influence HRQOL and should be addressed, behavioral characteristics may be better indicators of risk for poor future HRQOL and should also be targets for intervention.

This study represents an important step in identifying modifiable individual and environmental characteristics that predict future HRQOL; however, several limitations must be considered. Despite relatively high re-enrollment at Time 2, the sample size was limited due to recruitment at a single transplant center, and the small sample size limited the number of factors that could be examined. Also, more than half of the sample was comprised of kidney transplant recipients, so results are more representative of that patient group. Although we did not find any significant associations between time since transplantation and HRQOL, the large range of time since transplantation within our sample is a limitation, as is the broad range of time between assessments (12–20 months). Finally, at Time 2 the CHQ was used with adolescents who were older than the age range for which the measure was originally designed. However, the use of the measure at both time periods allowed for longitudinal comparisons.

Future research in this area should examine the impact of a broader range of individual and environmental factors on HRQOL, such as coping behaviors, parental factors, influence of peers, and school factors. For example, examining family conflict specific to medication adherence and healthcare, as opposed to general family conflict, may elucidate the relationships among these factors and HRQOL. Mediation models could be tested to identify causal relationships among factors. Additionally, following families beginning prior to transplant can determine whether various demographic, individual, and environmental characteristics exert the same influence at various important time points relative to transplant. Multi-site investigations are imperative to obtain larger and more representative samples of each organ group.

In conclusion, the results of this study suggested that several individual and environmental factors were predictive of future HRQOL in adolescent transplant recipients. Transplant centers should routinely evaluate for risk factors of poorer HRQOL. In particular, low income, greater number of rescheduled clinic appointments, poorer medication adherence, and greater family conflict predicted poorer future physical functioning and mental health.

Higher income, fewer rescheduled clinic appointments, the presence of a rejection episode, and greater family conflict predicted poorer general health perceptions. Interventions aimed to improve consistency in attending clinic appointments, family conflict, and adherence may help improve adolescent long-term HRQOL, though further research is needed to evaluate these proposed associations. In other pediatric populations, family-based interventions have been shown to improve family conflict and adherence (e.g., Anderson, Brackett, Ho, & Laffel, 1999; Wysocki et al., 2006). In pediatric liver transplant recipients, non-controlled trials of adherence-promoting programs showed promising results, indicating improvements in some medical outcomes (e.g., Shemesh et al., 2008). Greater attention to evaluating interventions is needed. Transplant teams may need a psychologist or social worker to assist in identifying and treating or referring families with risk factors to promote optimal HRQOL.

Supplementary Data

Supplementary data can be found at: http://www.jpepsy.oxfordjournals.org/

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Data from Time 1 of this longitudinal investigation were previously published (see Simons, Anglin, Warshaw, Mahle, Vincent, & Blount, 2008).

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References

Alonso, E. M., Limbers, C. A., Neighbors, K., Martz, K., Bucuvalas, J. C., Webb, T., & Warni, J. W. (2010). Cross-sectional analysis of health-related quality of life in pediatric liver transplant recipients. *Journal of Pediatrics, 156*, 270–276.

Alonso, E. M., Neighbors, K., Barton, F. B., McDiarmid, S. V., Dunn, S. P., Mazariegos, G. V., . . . Bucuvalas, J. C.; the Studies of Pediatric Liver Transplant Research Group. (2008). Health-related quality of life and family function following pediatric liver transplantation. *Liver Transplantation, 14*, 460–468.

Alonso, E. M., Neighbors, K., Mattson, C., Sweet, E., Ruch-Ross, H., & Berry, C. (2003). Functional outcomes of pediatric liver transplantation. *Journal of Pediatric Gastroenterology and Nutrition, 37*, 155–160.

Anderson, B., Brackett, J., Ho, J., & Laffel, L. (1999). An office-based intervention to maintain parent-adolescent teamwork in diabetes management. *Diabetes Care, 22*, 713–721.

Anthony, S. J., BarZiv, S. P., & Ng, V. L. (2010). Quality of life after pediatric solid organ transplantation. *Pediatric Clinics of North America, 57*, 559–574.

Bucuvalas, J., Britto, M., Krug, S., Ryckman, F. C., Atherton, H., Alonso, M. P., . . . Kotagal, U. (2003). Health-related quality of life in pediatric liver transplant recipients: A single-center study. *Liver Transplantation, 9*, 62–71.

Butkus, D. E., Mayedrech, E. F., & Raju, S. S. (1992). Racial differences in the survival of cadaver renal allografts–overriding effects of HLA matching and socioeconomic factors. *New England Journal of Medicine, 327*, 840–845.

Cole, C. R., Bucuvalas, J. C., Hornung, R. W., Krug, S., Ryckman, F. C., Atherton, H., . . . Kotagal, U. (2004). Impact of liver transplantation on HRQOL in children less than 5 years old. *Pediatric Transplantation, 8*, 222–227.

Cruz, I., Marciel, K. K., Quittner, A. L., & Schechter, M. S. (2009). Anxiety and depression in cystic fibrosis. *Seminars in Respiratory and Critical Care Medicine, 30*, 569–578.

De Civita, M., Regier, D., Alamgir, A. H., Anis, A. H., Fitzgerald, M. J., & Marra, C. A. (2005). Evaluating health-related quality-of-life studies in paediatric populations: Some conceptual, methodological and developmental considerations and recent applications. *Pharmacoeconomics, 23*, 659–685.

Devine, K. A., Reed-Knight, B., Simons, L. E., Mee, L., & Blount, R. L. (2010). Prospective comparison of parent and adolescent report of health-related quality of life in adolescent solid organ transplant recipients. *Pediatric Transplantation, 14*, 1000–1006.

DiMatteo, M. R. (2004). Social support and patient adherence to medical treatment: A meta-analysis. *Health Psychology, 23*, 207–218.

Ferrans, C. E., Zerwic, J. J., Wilbur, J. E., & Larson, J. L. (2005). Conceptual model of health-related quality of life. *Journal of Nursing Scholarship, 37*, 336–342.

Franke, G. H., Reimer, J., Kohnle, M., Luetkes, P., Maehner, N., & Heemann, U. (1999). Quality of life in end-stage renal disease patients after successful kidney transplantation: Development of the ESRD Symptom Checklist-Transplantation Module. *Nephron, 83*, 31–39.

Fredericks, E. M., Lopez, M. J., Magee, J. C., Shieck, V., & Opipari-Arrigan, L. (2007). Psychological functioning, nonadherence and health outcomes after pediatric liver transplantation. *American Journal of Transplantation, 7*, 1974–1983.

Fredericks, E. M., Magee, J. C., Opipari-Arrigan, L., Shieck, V., Well, A., & Lopez, M. J. (2008). Adherence and health-related quality of life in adolescent liver transplant recipients. *Pediatric Transplantation, 12*, 289–299.

Hassan, K., Loar, R., Anderson, B. J., & Heptulla, R. A. (2006). The role of socioeconomic status, depression, quality of life, and glycemic control in type 1 diabetes mellitus. *The Journal of Pediatrics, 149*, 526–531.

Hollifield, M., Paine, S., Tuttle, L., & Kellner, R. (1999). Hypochondriasis, somatization, and perceived health and utilization of health care services. *Psychosomatics, 40*, 380–386.

Kaufman, M., Shemesh, E., & Benton, T. (2010). The adolescent transplant recipient. *Pediatric Clinics of Noth America, 57*, 575–592.

Landgraf, J. M., Abetz, L., & Ware, J. E. (1999). *The CHQ user's manual* (2nd edn). Boston, MA: HealthAct.

Modi, A. C., & Quittner, A. L. (2003). Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. *Journal of Pediatric Psychology, 28*, 535–546.

Moos, R. H., & Moos, B. S. (1994). *Manual for the Family Environment Scale*. Palo Alto, CA: Consulting Psychologists Press.

Palermo, T. M., Long, A. C., Lewandowski, A. S., Drotar, D., Quittner, A. L., & Walker, L. S. (2008). Evidence-based assessment of health-related quality of life and functional impairment in pediatric psychology. *Journal of Pediatric Psychology, 33*, 983–996.

Reed-Knight, B., Lewis, J. D., & Blount, R. L. (2010). Association of disease, adolescent, and family factors in pediatric inflammatory bowel disease. *Journal of Pediatric Psychology*. Advance online publication. doi:10.1093/jpepsy/jsq076.

Rianthavorn, P., & Ettenger, R. B. (2005). Medication non-adherence in the adolescent renal transplant recipient: A clinician's viewpoint. *Pediatric Transplantation, 9*, 398–407.

Shemesh, E., Annunziato, R. A., Shneider, B. L., Dugan, C. A., Warshaw, J., Kerkar, N., & Emre, S. (2008). Improving adherence to mediations in pediatric liver transplant recipients. *Pediatric Transplantation, 12*, 316–323.

Simons, L. E., Anglin, G., Warshaw, B. L., Mahle, W. T., Vincent, R. N., & Blount, R. L. (2008). Understanding the pathway between the transplant experience and health-related quality of life outcomes in adolescents. *Pediatric Transplantation, 12*, 187–193.

Simons, L. E., & Blount, R. L. (2007). Identifying barriers to medication adherence in adolescent transplant recipients. *Journal of Pediatric Psychology, 32*, 831–844.

Sundaram, S. S., Landgraf, J. M., Neighbors, K., Cohn, R. A., & Alonso, E. M. (2007). Adolescent health-related quality of life following liver and kidney transplantation. *American Journal of Transplantation, 7*, 982–989.

Taylor, R. M., Franck, L. S., Gibson, F., Donaldson, N., & Dhawan, A. (2009). Study of the factors affecting health-related quality of life in adolescents after liver transplantation. *American Journal of Transplantation, 9*, 1179–1188.

Wilson, I. B., & Cleary, P. D. (1995). Linking clinical variables with health-related quality of life: A conceptual model of patient outcomes. *Journal of the American Medical Association, 273*, 59–65.

Wysocki, T., Harris, M. A., Buckloh, L. M., Mertlich, D., Lochrie, A. S., Taylor, A., . . . White, N. H. (2006). Effects of behavioral family systems therapy for diabetes on adolescents' family relationships, treatment adherence, and metabolic control. *Journal of Pediatric Psychology, 31*, 928–938.

Zelikovsky, N., & Schast, A. (2008). Eliciting accurate reports of adherence in a clinical interview: Development of the medical adherence measure. *Pediatric Nursing, 34*, 141–146.