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Keywords: Adolescents, VSP-A, Structural equation modeling

Objective To investigate the determinants of quality of life (QoL) in children with inborn errors of metabolism with restricted diet (IEMRDs) using a single theory-based multidimensional model.

Study design In this multicenter cross-sectional study, data from children with IEMRDs (except phenylketonuria) aged 8 to 17 years and their parents were collected from January 2015 to December 2017. Measurements included a child's self-reported QoL, self-rated behavioral problems and anxiety, and parental anxiety. Based on hypotheses from a literature-built theoretical model linking demographic, clinical, family environment and psychosocial characteristics to QoL either directly or indirectly, associations of these factors with a child's self-rated QoL were examined using a structural equation modeling (SEM) approach.

Results A total of 312 children (mean [SD] age, 12.2 [2.6] years; 160 [51%] boys) were included. Higher trait anxiety and behavioral problems in children were the most important factors associated with poorer QoL (standardized path coefficients = −0.71 and −0.23, respectively). Additionally, higher parent trait anxiety, younger age at diagnosis, and having a disease requiring an emergency diet were associated with poorer QoL in these children. The final model fit the data closely according to conventional goodness-of-fit statistics and explained 86% of QoL variance.

Conclusions Psychosocial factors appear to be major determinants of QoL impairment in children with IEMRDs. These factors should be particularly addressed in clinical practice as part of the global treatment plan for a child with IEMRD. Future studies based on longitudinal design should consider coping strategies when exploring potential predictive factors of QoL. Trial registration ClinicalTrials.gov: NCT02552784

Inborn errors of metabolism with restricted diet (IEMRDs) are a heterogeneous group of genetic diseases affecting metabolic pathways and require adherence to specific and lifelong restricted diets.[1,2] These diets, designed to control intoxication due to enzyme deficiency or to bypass the metabolic block providing an alternative source of energy, may switch to an emergency diet to adapt to exogenous circumstances associated with acute catabolism which could lead to clinical and biological decompensation. Although IEMRDs are rare, collectively they account for a significant proportion of neonatal and childhood morbidity and mortality, with an overall estimated incidence of 1 in 800-2500 live births [3,4] and a global death rate of 0.4% of all childhood deaths worldwide.[5] Patients with IEMRDs may present with lifelong, diverse acute or progressive clinical manifestations including metabolic decompensations, multiorgan impairments, neurologic abnormalities, developmental delays, and behavioral and intellectual disabilities. [6,7] These individuals have to deal with disease complications that may have physical and psychological effects. Assessing their quality of life (QoL) is recommended as this could be a useful complement to managing pathophysiological symptoms. [8]

Young patients with IEMRD have impaired QoL compared with a general reference population. [2,9–13] Few studies have explored QoL determinants in IEMRD context, and these investigations were based mainly adult populations. [14–16] The few studies on children have focused on specific diseases such as intoxication-type inborn errors of metabolism [13,17] or were limited to a small sample size.[2] Identified determinants in these studies [2,13,17] were child's age, parent's employment, and disease-related characteristics such as eating disorders, diet regimen, feeding modalities, and neurologic complications. Other predictors of children's QoL impairment in other chronic diseases include children's higher behavioral problems [18,19] and anxiety either in children [20] or parents. [21] Although some studies have pointed out the behavioral and emotional problems in families affected by IEMRDs [10,22,23], no specific reports have assessed the relative contribution of these factors on children's QoL. Moreover, clinical

characteristics such as age at diagnosis and disease severity may influence QoL, although the corresponding evidence has been mixed.[13,24,25]

From a methodological perspective, all these studies used analytical approaches that failed to simultaneously assess both direct and indirect effects of QoL determinants and their interrelationships. Furthermore, parameter estimates could be biased in those analyses due to a failure to account for measurement errors.[26] To address these issues, structural equation modeling (SEM) [26], a flexible multivariate approach for modeling complex relationships involving latent variables, could be used to explore determinants of QoL as a multidimensional construct.

The objective of this study was to investigate demographic, clinical, family and psychosocial factors as potential determinants of QoL in children with an IEMRD through a theoretical model using a SEM approach.

Methods

A large observational multicenter study was set up to describe the objective and perceived health status in children with an IEMRD followed in 14 French university hospitals certified as reference or competence centers for Inborn Errors of Metabolism (IEM) healthcare which involve systematically specialized clinicians and dieticians. [12] The inclusion criteria were a patient with an IEMRD followed at one of the 14 participating centers; whose diagnosis was made after January 2000, the date at which healthcare for IEMRDs was standardized; age < 18 years at inclusion. The study screened 633 patients, of whom 578 were enrolled. The study was approved by the French Ethics Committee (Comité de Protection des Personnes Sud Méditerranée V), the French National Agency for Medicines and Health Products Safety, and by the French data protection authority (Commission Nationale de l'Informatique et des Libertés). Informed written consent was obtained for all participants from their 2 parents or

from their legal representatives. The protocol was registered in ClinicalTrials.gov (number: NCT02552784).

A subset of participants in this study were selected for this cross-sectional ancillary study, which was designed to examine factors that may influence QoL in children with an IEMRD (Table I; available at www.jpeds.com). Children 8 to 17 years who had at least one parent who returned the questionnaire were included.

The data collection process has been previously described. [12] Briefly, children and their parents completed a questionnaire either at a planned visit or at home. Questionnaires included children's self-rated measurements (anxiety, behavioral difficulties and QoL), and parents' reported measurements (demographics, family environment characteristics, and parental anxiety). Children's clinical and healthcare data were obtained from a separate questionnaire completed by the investigating physician (Table 2; available at www.jpeds.com).[27–33]

Children's QoL was assessed using the self-administered questionnaire "Vécu et Santé Perçue de l'Adolescent" (VSP-A), which was developed and validated in French. [34,35] Versions designed for 8 to 10-year-old children (38 items version-VSP-Ae) or 11 to 17-year-old adolescents (39 items version-VSP-A) were used according to the biological age of the participants and customized to describe an index and eight dimensions (vitality, general well-being [psychological and physical well-being], relations with friends, leisure activities, relations with parents/family, school performance, self-esteem, and relations with medical staff). Each item was answered on a 5-point Likert scale. The score of each dimension was computed as the mean of constitutive items. All scores were linearly transformed to a 0 - 100 scale, with higher scores reflecting better QoL. Internal consistency of this scale ranges from 0.74 to 0.91. [36] QoL was built as a latent variable that did not include the relationships with medical staff. This dimension was dropped from the QoL construct because of a negative

factor loading contrasting with all others. Therefore, the QoL construct included seven dimensions.

Hypotheses

Given the lack of data on QoL determinants in children with IEMRDs, we constructed hypothetical relationships between factors by examining previously published research in children with other chronic diseases. Disease clinical characteristics, sex, age, and family socioeconomic status have previously been shown to be directly linked to child QoL. [24,37–39] Therefore, it was hypothesized that these factors would significantly influence QoL in children with IEMRDs.

Parent's anxiety was found to be a significant predictor of children's QoL. [21,40] Therefore, we suggested that higher parental anxiety would negatively impact QoL in children with IEMRDs.

Based on the findings of Adams et al and Moreira et al, we hypothesized that higher anxiety in children would be a factor negatively contributing to their QoL in the IEMRD context. [20, 41] Given the previous works of Barthel et al and Otto et al, it was also hypothesized that greater behavioral difficulties in children with IEMRDs would negatively influence their QoL.[38,39] It has also been established that disease clinical characteristics, sex, age, and family socioeconomic status were associated with child behavior [42,43] and child trait anxiety. [44,45] Therefore, it was expected that these factors would significantly impact child behavior and trait anxiety in children with IEMRDs.

According to the previous works of Toledano-Toledano et al and Zhou et al, we hypothesized that disease clinical characteristics, sex, age, and family socioeconomic status would significantly influence parental anxiety in the IEMRD context. [46,47]

Statistical analyses

Descriptive analysis was conducted to summarize participants' characteristics with qualitative variables presented as numbers and percentages and quantitative variables as means and standard deviations (SD). Correlations were performed to explore the strength of the relationships between the continuous variables using the Pearson correlation test. Structural equation modeling (SEM) using lavaan R package version 0.6-8 [48] was performed to investigate the relationships among variables and to test whether the theoretical model fit the data. Our model was based on a latent variable from seven indicators (ie, the seven dimensions involved in the child's QoL construct), and 13 observed explanatory variables (Table 2). Maximum likelihood estimation with full information maximum likelihood (FIML) was used to handle missing data. Due to the multivariate non-normality of the endogenous variables, the maximum likelihood estimator with robust standard errors (MLR) for model parameters estimation was used. [26] Next, the overall model fit was assessed using the robust root mean square error of approximation (RMSEA), with an expected value lower than 0.06, the robust comparative fit index (CFI), and the robust Tucker-Lewis index (TLI) with expected values higher than 0.90. [49] The initial path model was modified by adding plausible and theoretically justifiable paths using modification indices. All of the hypothesized paths in the conceptual model were tested but, only significant paths were shown in the final results. Statistical analyses were performed using R software, version 4.0.5.[50] Statistical significance was defined as $P < 0.05$.

Results

Sample characteristics

Among the 578 patients previously enrolled from January 2015 to December 2017, 262 children aged < 8 years were excluded from the study. Of the 316 eligible children, four children for whom no parent returned the questionnaire were excluded. Ultimately, 312 children aged 8-17 were included (Table 3). The mean age at inclusion was 12.2 years (SD:

2.6) and 51.3% were boys. Of the participants, 75% of the children's parents were living together and the family wealth was rated as high by 55.4% of the children. The correlations between observed variables are shown in Table 4 (available at www.jpeds.com).

Structural equation model

Model evaluation - Modification

The initial theoretical model (Figure 1) did not result in good fit to the data (χ^2 (91) = 194.2, $P < .001$; CFI = 0.89; TLI = 0.81; RMSEA = 0.06). After considering the result of this initial model and based on theoretical supports, some pathways suggested by the modification indices were considered. Thus, additional paths from "child trait anxiety", "child prosocial behavior" and "child total difficulties" to "parent trait anxiety" were introduced, resulting in a modified model (Figure 1), which was reestimated. Subsequently, few paths that contributed to poor fit were removed. The final result of the structural equation model (Figure 2) showed good fit indices with a CFI=0.96, a TLI=0.94, an RMSEA=0.04; and the standardized root mean ratio (SRMR) was lower than 0.1 indicating a close-fit of our model to the data.

Direct effects

SEM results revealed that the child's age at diagnosis and the potential need of an emergency diet were significantly associated positively and negatively, respectively, with the child's QoL ($\beta = 0.12$ and -0.15). Parents' trait anxiety was significantly negatively associated with the child's QoL ($\beta = -0.16$). A strong significant negative association was found between child anxiety and QoL ($\beta = -0.71$) along with a significant negative moderate association between child total difficulties and QoL ($\beta = -0.23$). Additionally, clinical characteristics such as a mixed or exclusively enteral feeding was positively associated with child total difficulties, and the potential need of an emergency diet was negatively associated with child trait anxiety.

However, paths from child's sex, feeding modality, disease complications, family affluence scale, family structure, and siblings to QoL were not significant, as indicated in Table 5, which presents all the tested path results.

A sensitivity analysis using bootstrapped standard errors and confidence intervals gave equivalent results except for parental anxiety effect on QoL, which shifted towards non-significance ($p = 0.06$).

Indirect effects

Results of indirect effects testing are presented in Table 6 (available at www.jpeds.com). The total indirect effect of emergency diet on QoL was significantly positive ($\beta = 0.15$, $p = 0.005$), which consists of two specific indirect effects via child trait anxiety ($\beta = 0.14$, $p = 0.004$) and via child trait anxiety and then via parent trait anxiety ($\beta = 0.006$, $p = 0.16$). The effect of feeding modality on QoL showed an identical trend, with a negative significant total indirect effect ($\beta = -0.04$, $p = 0.03$) and a non-significant total effect ($\beta = 0.04$, $p = 0.54$).

Finally, 86% of QoL's variance in patients with IEMRD could be explained by the model.

Discussion

This study examined the impact of demographic, clinical, family, and psychosocial factors as potential determinants of QoL among children with IEMRD within a single multidimensional model. The study used a SEM approach that allowed simultaneous assessment of a set of relationships among these potential determinants and children's QoL. The model showed a close fit to the data supporting the postulated relations among variables.

Anxiety and behavioral difficulties in children with IEMRD are the most important features influencing their QoL, higher parental trait anxiety is related to poorer QoL in these children; and clinical characteristics, i.e., younger age at diagnosis and presenting a disease requiring an emergency diet, were associated with poorer QoL after controlling for other factors.

Psychosocial and behavioral factors impacting QoL

Consistent with previous studies on children with chronic conditions [20,41,51], we found that child anxiety was negatively associated with QoL. Anxiety is a psychosocial issue common to patients living with IEMRDs and it deserves attention because of its real impact on the daily lives of affected children and their families. [23] Vliet et al explored QoL in tyrosinemia type 1 patients and found that almost half of children had internalizing problems, mainly anxiety, which was negatively associated with child's QoL.[52] Patients with IEMRDs experience specific psychosocial concerns contrasting with other chronic diseases. These patients are faced to limited social outing and independence along with isolation from peers due to the lifelong strain of dietary management as well as ongoing metabolic decompensation and its associated death risk.[22] QoL was more impacted by child anxiety than by the other factors, implying that anxiety may be the most important determinant of IEMRDs children's QoL in our study.

Child behavioral difficulties were negatively related to QoL in line with findings from a population-based study on emotional well-being and behavior [53] and studies in chronically ill children and adolescents. [38,54] However, Jamiolkowski et al reported no association in the context of IEMRDs.[10] A possible explanation for this discrepancy could be that these authors included only two groups of IEMRDs, i.e., organic aciduria and urea cycle disorders with small sample sizes, leading to the use of combined proxy and self-reported behavioral problems assessments. Behavioral problems are common in children with IEMRDs [55,56] and can potentially impact health and well-being negatively. [52] These children may also present cognitive impairments [55], which could cause those behavioral problems as previously described. [10] In the specific context of IEMRDs, it could be hypothesized that the underlying metabolic disorder could be a common cause resulting in two co-occurring effects. Indeed,

behavioral and cognitive difficulties associated with IEMRDs could be due to an acute and/or chronic metabolic intoxication of the central nervous system or treatment-related strain. [57,58] Children with behavioral problems may be less able to adapt to daily demands and may have higher difficulties in social integration, enhanced by poor social support. [53]

Our results indicated that high parental trait anxiety negatively affects children's QoL, as previously reported. [21,40,59] Parental psychosocial problems including higher general stress, depression and anxiety have been found to negatively influence well-being in children with cerebral palsy [60] and type 1 diabetes. [61] Anxiety is common among parents of children with an IEMRD and may be due to child's diet therapy.[62] Given the caregiving demand, parents of children with IEMRDs may find less time for themselves and their other children, contributing to enhance their emotional and mental stress.[63] Consequently, distressed parents may create a negative environment around their children, which could affect those children's QoL.

Psychosocial and behavioral issues in children with IEMRDs therefore require careful identification and treatment because these factors undermine their QoL. Despite existing care involving child psychologists, psychosocial factors remain the most important determinants impairing QoL. As modifiable factors, these psychosocial determinants should be targeted by appropriate clinical and social intervention including therapeutic patient education, which is critical to enhance disease daily self-management skills and minimize stressors for both patients and their families.

Clinical factors affecting QoL

Younger age at diagnosis was significantly associated with poorer QoL. Existing literature highlights the various relationships between age at diagnosis and QoL. Although some report increased age at diagnosis is associated with better QoL [64], others do not support this

relationship. [13,25] In our study, half of the children were diagnosed before the age of six months. The early age at diagnosis in IEMRDs may indicate the intensity of early symptoms and is therefore essential to avoid delays in initiating treatment because therapies are available for a large proportion of these diseases. Furthermore, we found that presenting a disease requiring an emergency diet was associated with an impaired QoL in children with IEMRDs. Most often, the cornerstone of treatment in IEMRDs is dietary and patients with a disease requiring an emergency diet are those at higher risk of metabolic decompensation [10], with increased caregiving demands and decreased participation in peer and school-based activities.[9]

Demographic and family factors were not associated with differences in child QoL. Although difference in children's QoL according to sex was previously described in chronically ill children [38,39], we did not found such a trend in our data. Living with a single parent or in a family with high material wealth did not influence child's QoL. There is limited evidence regarding the association between family structure and children's QoL with discrepant findings. [65,66] Additionally, we would expect that families with higher material wealth might have access to more resources and then contribute to more social support to their child, however, no association was found.

Indirect effects testing indicated that emergency diet has a positive indirect effect on QoL. In contrast, its direct impact was negative, suggesting undiscovered or omitted mediators, [67] possibly coping skills [68]. Moreover, mixed and/or exclusively enteral feeding did not contribute directly to QoL impairment but did so indirectly through behavioral difficulties, possibly because children with this feeding modality could experience more behavioral challenges such as limited relationships with peers, resulting in poorer QoL.

Strengths and limitations

First, phenylketonuria was not included in this study because, in this intoxication-type IEMRD, which has been part of the newborn screen in France since the 1970s, children and their parents are not initially challenged with disease symptoms. Moreover, as early treatment is available with no associated risk of metabolic decompensation, the outcome of these patients is overall favorable. Second, the cross-sectional design of this study does not allow inferences about causality. Some associations may have been overlooked due to the high heterogeneity of the IEMRDs. Some of these diseases vary greatly in severity and are experienced differently between patients and within families. However, these diseases share diets, feeding modalities and complications as characteristics. Biological age was used to identify the relevant QoL questionnaire even though cognitive age could also be considered. Cognitive age was not available in the survey, and the only information that could have been used was the result of neuropsychological testing, which was rarely performed (i.e., in approximately 15% of participants).

Third, owing to the high rate of missing responses to child self-coping assessments (almost 50%), which was higher than those reported by others [69], this factor was not included in the analysis even though the use of coping strategies has been reported to be a determinant of QoL in children with chronic pediatric health conditions. [70] This high rate of non-completion could be explained by the complex structure of the scale used, which requires simultaneous evaluation of items' frequency and efficacy. Also, as previously noted, a degree of verbal competence is required for children to understand the questions and verbalize their thoughts to complete the KIDCOPE checklist.[71] Finally, completing this instrument requires substantial visual and time efforts in addition to the attention needed. [72] Future research might investigate this issue.

Fourth, some data considered as sensitive (such as ethnic origin of the patients, or whether they were native French or immigrants) were not reported and according to the principles of the French Data Protection Authority, they were not measured in this study.

Even though IEMRDs are rare diseases, our study included a relatively large sample covering almost the entire patient active file. Structural equation modeling is theory and data-driven, and the final model is a plausible one among others that might be more accurate [26]. Besides the goodness of fit from statistical perspectives, our model made substantive sense with meaningful interpretation. Nevertheless, future research based on different populations should test this model. Moreover, our model explained 86% of QoL variance in children with IEMRDs, suggesting that the major factors that could explain QoL in the IEMRDs context were considered. Further, our study and results provide information for clinical practice and future research on psychosocial determinants and clinical factors related to QoL in children with IEMRDs.

Our study suggests that psychosocial factors are more important QoL determinants than clinical variables such as IEMRD type and age at diagnosis in children with IEMRDs. These factors can potentially be used as screening measures to help identify IEMRD patients who may be at risk of impaired QoL in clinical practice and should be targeted to enhance QoL in health promotion initiatives.

Abbreviations:

- IEMRD: inborn error of metabolism with restricted diet
- QoL: quality of life
- SEM: structural equation modeling
- VSP-A: Vécu et Santé Perçue des Adolescents

- RMSEA: root mean square error of approximation
- CFI: comparative fit index
- TLI: Tucker Lewis index

Figure Legend

Figure 1. Hypothesized models tested for A, initial model based on literature; and for B, modified final model fit to the data.

In B, dashed arrows are paths added to initial hypothesized model suggested by modifications indices and theoretical supports.

Figure 2. Final structural model with standardized estimates (N=312)

* P < 0.05; ** P < 0.01; *** P < 0.001

Robust chi square = 155.33; Degrees of freedom = 112; Normed Robust chi square = 1.39; p-value for Robust chi square = 0.004

Robust CFI = 0.956; Robust TLI = 0.936

Robust RMSEA = 0.035 (90% CI = 0.020 - 0.048); P-Close= 0.967

SRMR = 0.052.

R^2 : % of QoL explained by the model

QoL: Child self-reported quality of life; General WB: General well-being

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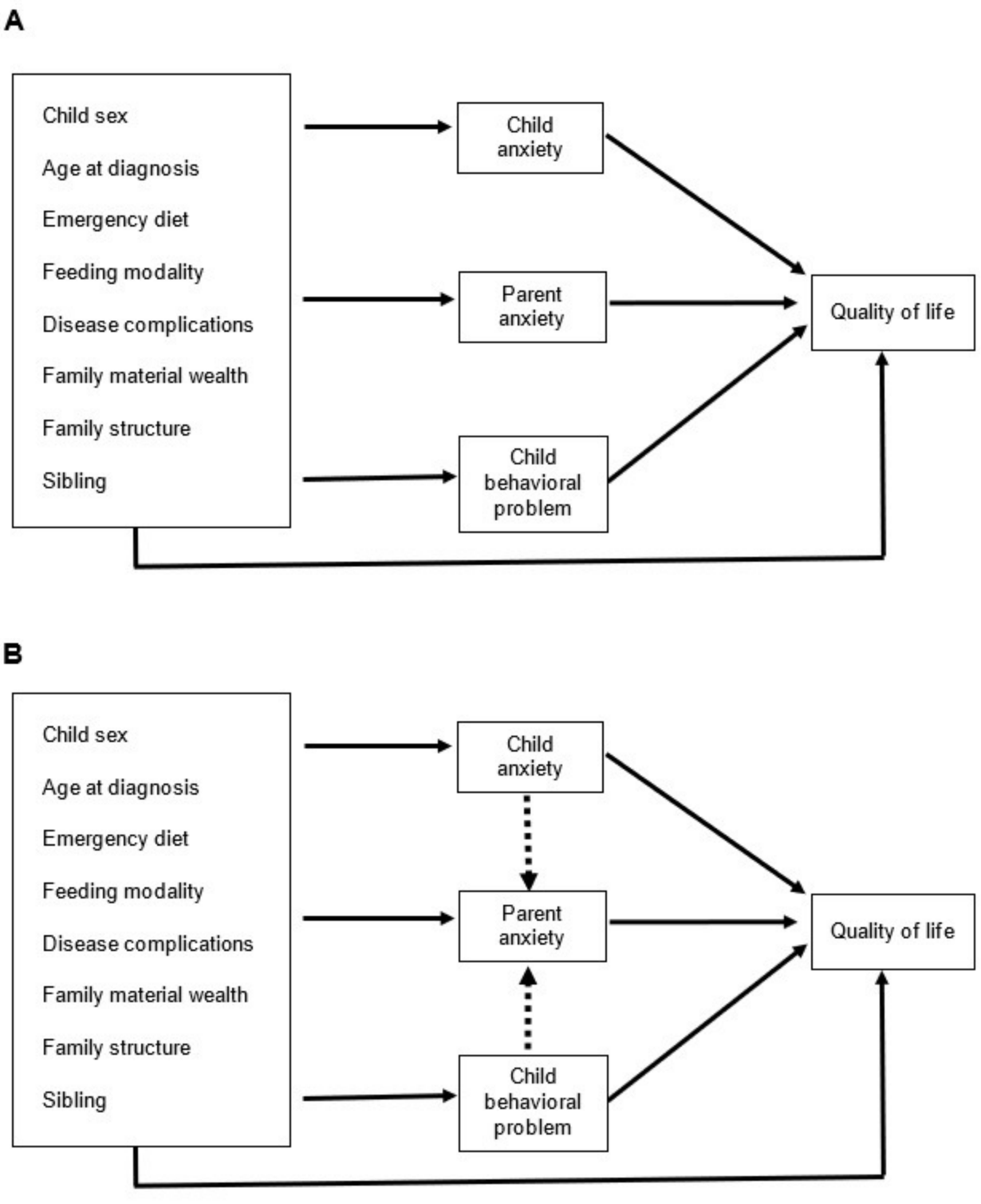
A
Child sex
Age at diagnosis
Emergency diet
Feeding modality
Disease complications
Family material wealth
Family structure
Sibling
Child anxiety
Parent anxiety
Child behavioral problem
Quality of life
B
Child sex
Age at diagnosis
Emergency diet
Feeding modality
Disease complications
Family material wealth
Family structure
Sibling
Child anxiety
Parent anxiety
Child behavioral problem
Quality of life

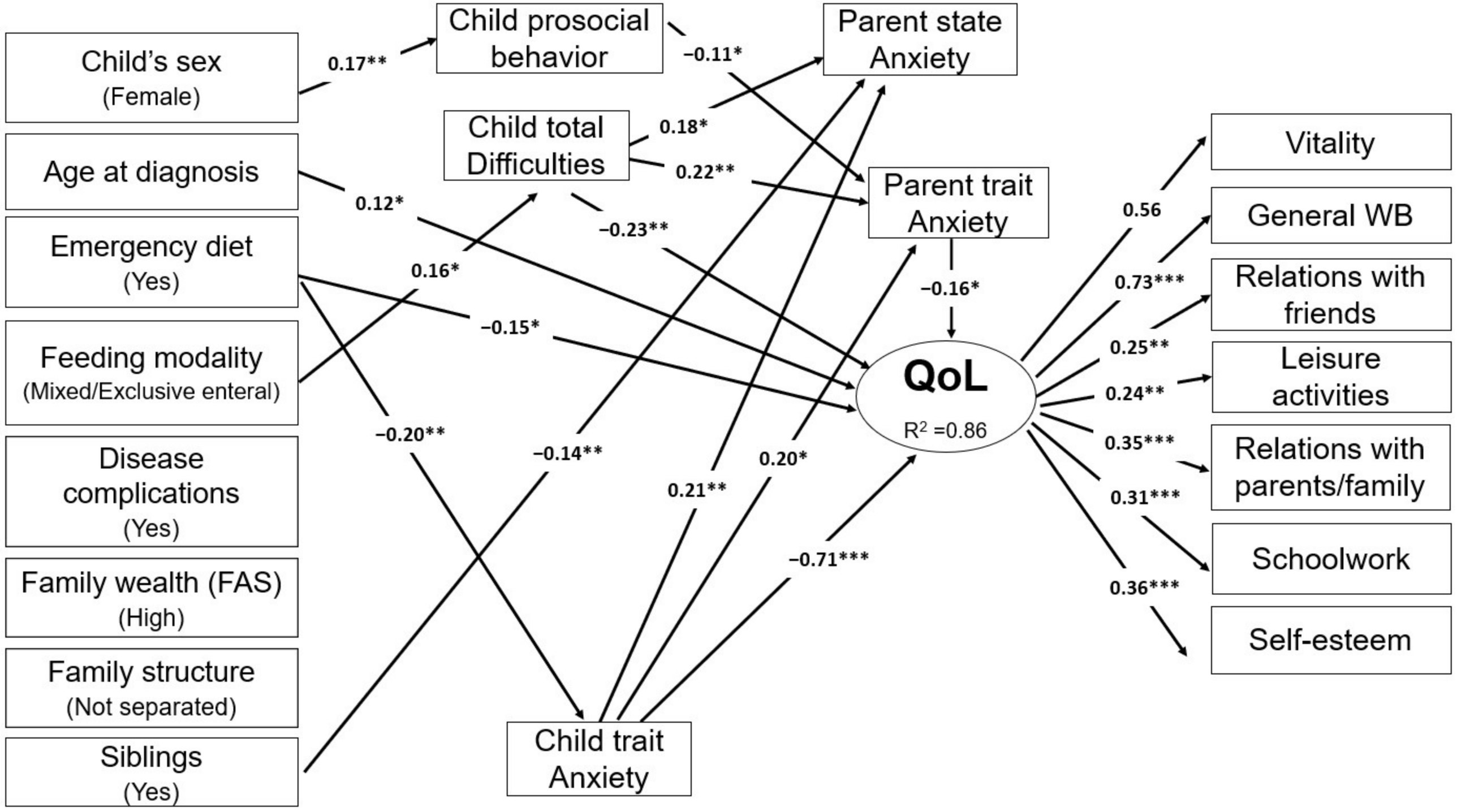
Child's sex
(Female)
Age at diagnosis
Emergency diet
(Yes)
Feeding modality
(Mixed/Exclusive enteral)
Disease complications
(Yes)
Family wealth (FAS)
(High)
Family structure
(Not separated)
Siblings
(Yes)
Child prosocial behavior
Child total Difficulties
Child trait Anxiety
Parent state Anxiety
Parent trait Anxiety
QoL
R2 =0.86
Vitality
General WB
Relations with friends
Leisure activities
Relations with parents/family
Schoolwork
Self-esteem
0.17**
−0.11*
0.18*
0.22**
0.12*
−0.23**
0.16*
−0.15*
−0.20**
−0.14**
0.21**
0.20*
−0.71***
−0.16*
0.56
0.73***
0.25**
0.24**
0.35***
0.31***
0.36***

Table 1. Included inborn errors of metabolism with restricted diet.

Type of inborn errors of metabolism with restricted diet	N
With emergency diets	**242**
With protein-restricted diets	**178**
Urea cycle disorders	73
N-Acetyl glutamate synthase (NAGS) deficiency	4
Carbamoylphosphatase synthetase 1 (CPS1) deficiency	7
Ormithine transcarbamylase (OTC) deficiency	32
Argininosuccinate synthetase deficiency	12
Argininosuccinate lyase deficiency	6
Arginase deficiency	4
Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome	3
Dibasic protein intolerance	5
Deficiency of an enzyme involved in amino acid(s) catabolism	105
Leucinosis	23
Organic acidurias	61
Methylmalonic acidemia	26
Propionic acidemia	24
Isovaleric aciduria	11
Glutaric aciduria type 1	14
Classic homocystinuria	7
With lipid-restricted diets	**26**
Carnitine palmitoyl transferase 1 (CPT1) deficiency	1
Carnitine palmitoyl transferase 2 (CPT2) deficiency	5
Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency	6
Long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency	6
Mitochondrial trifunctional protein deficiency	1
Multiple acyl-CoA dehydrogenase deficiency	1
HMG-CoA lyase deficiency	3
HMG-CoA synthase deficiency	-
Short-chain acyl-CoA dehydrogenase (SCAD) deficiency	1
Beta-ketothiolase deficiency	2
Other diets	**38**
Glycogen storage disorders type I	21
Glycogen storage disorders type III	8
Glycogen storage disorders type VI	1
Glycogen storage disorders type IX	4
Other diseases with emergency diet	4
Without an emergency diet	**70**
With a ketogenic diet	**15**
Cerebral glucose transporter deficiency syndrome	9
Pyruvate dehydrogenase deficiency	6
Other diets	**55**
Tyrosinemia	12
Galactosemia	27
Fructosemia	11
Fructose-1,6-bisphosphase deficiency	3
Other diseases without emergency diet	2

Table 2. Collected measurements (Clinical and healthcare data, family environment data, psychosocial and behavioral data)

Clinical and healthcare data	
Demographic	Sex of the child
Clinical data	
Type of IEMRD	With versus without potential need for emergency diet.
Feeding modality at inclusion	Exclusively oral versus exclusively enteral / mixed oral-enteral
Disease complication	No complication versus at least one current clinical complication, (neurocognitive, renal, muscular, ophthalmic, hepatic, cardiac, and respiratory)
Healthcare history	Age at diagnosis Time since diagnosis
Family environment data	
Sociodemographic data of the family	Family structure (i.e., parents living together or not) Siblings (i.e., affected child has any siblings or not)
Economic data of the family	Family material wealth assessed by the Family Affluence Scale [27,28], dichotomized into high versus average/low wealth level
Psychosocial and behavioral data	
Parent anxiety assessed by the adult version of the State-Trait Anxiety Inventory (STAI) [29]	Two 20-item scales for measuring state and trait anxiety. Total scores for state or trait anxiety range from 20 to 80 with higher scores indicating higher levels of anxiety. Internal consistency coefficients range from 0.86 to 0.95. [29]
Child behavioral problems self-assessed by the Strengths and Difficulties Questionnaire (SDQ) [30]	Two behavior types based on 5 subscales: total difficulties (sum of 4 subscales i.e., emotional symptoms, conduct problems, hyperactivity-inattention, peer problems) and prosocial behavior. Higher scores on the prosocial behavior subscale reflect strengths, whereas higher scores on the other four subscales reflect difficulties. Internal consistency is 0.73. [31]
Child anxiety self-assessed by an age-appropriate version of the STAI (STAI-C/ STAI-Y) [32]	Two subscales (state and trait anxiety) are available, but only the trait was assessed. Two age-based versions were used (child version: total range from 20 to 60; adolescent version: total range from 20 to 80). Total scores were normalized, ranking finally from 20 to 80 for all participants to account for scoring differences. Higher scores indicate higher anxiety symptoms. Internal consistency is 0.89. [33]

Table 3. Participant's characteristics (N= 312)

Variables	N= 312
Clinical and healthcare data	
Age at inclusion, mean (SD), y	12.2 (2.6)
8-12-y, n (%)	188 (60.3)
13-17-y, n (%)	124 (39.7)
Sex, n (%)	
Male	160 (51.3)
Female	152 (48.7)
IEMRD with emergency diet, n (%)	242 (77.6)
Feeding modality, n (%)	
Exclusively oral	259 (83.0)
Mixed oral-enteral or exclusively enteral	53 (17.0)
At least one complication, n (%)[a]	166 (53.2)
Neurocognitive	116 (37.2)
Renal	24 (7.7)
Muscular	23 (7.4)
Ophthalmic	23 (7.4)
Hepatic	22 (7.1)
Cardiac	15 (4.8)
Respiratory	2 (0.6)
Age at diagnosis, mean (SD), months	21.1 (36.7)
NA, n	2
Time since diagnosis, mean (SD), y	10.5 (3.7)
< 10 y	137 (44.2)
≥ 10 y	173 (55.8)
NA, n	2
Family environment	
Family structure (parents living together), n (%)	234 (75.0)
Child has siblings (yes), n (%)	271 (87.1)
NA, n	1
Family material wealth (FAS), n (%)	
Low/ Average	137 (44.6)
High	170 (55.4)
NA, n	5
Parents' psychosocial data	
State Anxiety (STAI-S), mean (SD)	35.1 (11.1)
NA, n	12
Trait Anxiety (STAI-T), mean (SD)	39.8 (10.5)
NA, n	14

Table 3. Participant's characteristics (N= 312) (continued).

Variables	N= 312
Children's psychosocial and behavioral data	
Strengths and Difficulties Questionnaire, mean (SD)	
Emotional symptoms	2.7 (2.3)
Conduct problems	2.3 (1.7)
Hyperactivity -inattention	4.0 (2.6)
Peer problems	2.2 (1.9)
Total difficulties	11.1 (5.8)
NA, n	60
Prosocial behavior	7.8 (1.9)
NA, n	60
Trait Anxiety (STAI-C/STAI-Y), mean (SD)	37.2 (9.3)
NA, n	57
Children's QoL (VSP-A), mean (SD)	
Index	67.0 (11.6)
NA, n	65
Vitality	72.9 (18.1)
NA, n	53
General well-being	73.2 (16.9)
NA, n	52
Relation with friends	55.9 (24.7)
NA, n	54
Leisure activities	50.9 (22.4)
NA, n	49
Relation with parents/family	68.7 (20.2)
NA, n	49
School work	67.2 (23.4)
NA, n	58
Self-esteem	79.4 (23.4)
NA, n	55

NA, not available.

[a] sum of complications (at least one) is lower than the sum of organ-related complications (i.e., neurocognitive, renal, muscular, ophthalmic, hepatic, cardiac and respiratory) due to some mixed organ-related complications.

Table 4. Correlation between observed variables

Observed variables [a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
1. Age at diagnosis	1.00												
2. Child total difficulties	–0.02	1.00											
3.Child prosocial behavior	0.08	**–0.29*** **	1.00										
4. Child trait anxiety	0.01	**0.57*** **	–0.12	1.00									
5. Parent state anxiety	–0.01	**0.32*** **	–0.12	**0.31*** **	1.00								
6. Parent trait anxiety	–0.02	**0.39*** **	**–0.24*** **	**0.33*** **	**0.80*** **	1.00							
7.Vitality	0.05	**–0.34*** **	**0.17** **	**–0.47*** **	**–0.20** **	**–0.25*** **	1.00						
8. General well-being	0.10	**–0.49*** **	0.09	**–0.62*** **	**–0.33*** **	**–0.35*** **	**0.36*** **	1.00					
9. Relation with friends	0.07	**–0.26*** **	**0.29*** **	**–0.13***	**–0.13***	**–0.19** **	**0.41*** **	0.03	1.00				
10. Leisure activities	0.07	–0.11	**0.13***	**–0.21*** **	–0.05	–0.09	**0.40*** **	0.10	**0.41*** **	1.00			
11. Relation with parents/family	0.03	**–0.23*** **	**0.15***	**–0.29*** **	–0.07	**–0.16** **	**0.42*** **	0.10	**0.23*** **	**0.21*** **	1.00		
12. School work	–0.04	**–0.27*** **	0.06	**–0.24*** **	**–0.16***	**–0.19** **	**0.36*** **	**0.18** **	0.11	0.12	**0.25*** **	1.00	
13. Self-esteem	–0.01	**–0.19** **	–0.05	**–0.32*** **	–0.11	–0.09	**0.19** **	**0.34*** **	–0.05	–0.03	0.11	0.06	1.00

[a] Observed variables from 7 to 13 are indicators of the QoL construct

[*] P < .05; [**] P < .01; [***] P < .001

Table 5. Standardized directs effects (regression coefficients) for the hypothesized model fitted to data, Final SEM results depicting the entire tested paths.

Dependent variables (Endogenous)	Independent variables (Endogenous/Exogenous)	Standardized direct effect	p-value
QoL	Child sex	0.020	0.70
	Age at diagnosis	0.120	0.04
	Emergency diet	−0.146	0.01
	Feeding modality	0.078	0.15
	Disease complications	−0.072	0.23
	Family material wealth	0.056	0.33
	Family structure	0.012	0.82
	Siblings	−0.044	0.39
	Child total difficulties	−0.225	0.002
	Child prosocial behavior	0.003	0.96
	Child trait anxiety	−0.711	< 0.001
	Parent state anxiety	0.002	0.98
	Parent trait anxiety	−0.163	0.048
Child total difficulties			
	Child sex	−0.112	0.07
	Emergency diet	−0.093	0.17
	Feeding modality	0.162	0.01
	Siblings	−0.016	0.82
Child prosocial behavior			
	Child sex	0.171	0.006
	Emergency diet	−0.036	0.57
	Feeding modality	−0.058	0.43
	Siblings	−0.010	0.87
Child trait anxiety			
	Child sex	0.054	0.38
	Emergency diet	−0.196	0.002
	Feeding modality	0.068	0.35
	Siblings	0.030	0.63
Parent state anxiety			
	Child total difficulties	0.179	0.02
	Child trait anxiety	0.211	0.008
	Siblings	−0.138	0.02
Parent trait anxiety			
	Child total difficulties	0.224	0.005
	Child prosocial behavior	−0.113	0.02
	Child trait anxiety	0.197	0.01
	Siblings	−0.112	0.05

Table 6. Standardized indirect and total effects tested, Results from SEM

Paths	Type of effect	Standardized estimate	p-value
Paths from emergency diet to QoL			
	Specific indirect effect via child trait anxiety	0.139	0.004
	Specific indirect effect via child trait anxiety and parent trait anxiety	0.006	0.16
	Total indirect effect	0.145	0.005
	Total effect	− 0.001	0.99
Paths from Feeding modality to QoL			
	Specific indirect effect via child total difficulties	− 0.037	0.04
	Specific indirect effect via child total difficulties and parent trait anxiety	− 0.006	0.17
	Total indirect effect	− 0.042	0.03
	Total effect	0.035	0.54
Path from Child sex to QoL			
	Specific indirect effect via child prosocial behavior and parent trait anxiety	0.003	0.20
	Total effect	0.024	0.66