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RESEARCH REPORT

Development and Psychometric Evaluation of the MetabQoL 1.0: A Quality of Life Questionnaire for Paediatric Patients with Intoxication-Type Inborn Errors of Metabolism

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Abstract *Introduction*: This study is part of the "European network and registry for intoxication type metabolic diseases" (E-IMD) project. Intoxication-type inborn errors of metabolism (IT-IEM) such as urea cycle disorders (UCD) and organic acidurias (OA) have a major impact on patients' lives. Patients have to adhere to strict diet and medication and may suffer from metabolic crises and neurocognitive impairment. Disease-specific health-related quality of life (HrQoL) assessment questionnaires are the method of choice to estimate the subjective burden of a

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disease. To date, no such instrument is available for IT-IEM.

Methods: Disease-specific patient- and parent-reported HrQoL questions were constructed in German based on focus group interviews with patients and parents. Questionnaires for patients from 8 to 18 years were piloted with 14 participants ($n = 9$ children and adolescents, $n = 5$ parents) by cognitive debriefing and tested psychometrically with 80 participants ($n = 38$ patients, $n = 42$ parents) for item characteristics, validity, and reliability to construct the first version of a disease-specific HrQoL questionnaire.

Results: Twenty-eight questions were selected based on item descriptives. Scales of self- and proxy questionnaires demonstrated acceptable to excellent reliability in terms of internal consistency (Cronbach's $\alpha = 0.70–0.93$). Scales and total scores correlated with those of generic HrQoL questionnaires, showing convergent validity.

Discussion: The MetabQoL 1.0 questionnaire exhibits sound psychometric properties and is a promising step towards assessing patient-reported outcomes in research and clinical practice. It provides a solid basis for translation into other languages and further elaboration and psychometric exploration in larger populations.

Introduction

This study is part of the "European network and registry for intoxication type metabolic diseases" (E-IMD) project, focusing on intoxication-type inborn errors of metabolism (IT-IEM) such as urea cycle disorders (UCD) and organic acidurias (OA). Estimated incidences are 1:35,000 for UCD (Summar et al. 2014) and 1:21,000 for OA (Dionisi-Vici et al. 2002). Recently, the natural course of the diseases has been described in two large samples (Kölker et al. 2015a; Kölker et al. 2015b; Waisbren et al. 2016). These reports highlight that IT-IEM have a major impact on patients' lives: Strict diet, daily intake of medication, the permanent risk of severe metabolic crises, and neurological sequelae are only some of the issues that the growing number of long-term surviving patients and their families face. Therefore, it is of utmost importance to consider health-related quality of life (HrQoL) as a major outcome parameter for this patient group besides medical and biochemical measures (Matza et al. 2004).

HrQoL is defined as "a patient's perception of the impact of disease and treatment on functioning in a variety of dimensions, including physical, psychological, and social domains" (Varni et al. 1999, p. 126). Due to the subjectivity of this construct, self-assessments by patients are the preferred data source (Matza et al. 2013). However, although self- and proxy assessments, e.g. by parents, often differ, parents can be very valuable as an additional source of information, especially in young or severely affected patients (Upton et al. 2008).

There are three main types of HrQoL assessment tools. Generic tools such as the PedsQL (Varni et al. 1999) target the general population and allow comparison between healthy individuals and individuals affected by any kind of disease. Chronic-generic tools such as the DISABKIDS (The DISABKIDS Group Europe 2006) allow more specific comparison between individuals affected by different diseases. Disease-specific tools such as the PKU-QOL (Regnault et al. 2015) investigate the impact of a particular disease or disease group on patients' life. They have shown high responsiveness to change of HrQoL (Wiebe et al. 2003) and are therefore the method of choice for measuring this outcome parameter in clinical trials or long-term patient management.

No such disease-specific instrument was available for IT-IEM (Zeltner et al. 2014). We therefore developed a questionnaire of this type, the MetabQoL 1.0, following the ISPOR Guidelines (Matza et al. 2013). Four versions were constructed: self- and parent reporting versions for patients from 8 to 18 years and adapted self- and parent reporting versions for patients younger than 8 years. The development process encompassed three main steps. First, focus group interviews were performed to identify core topics with high content validity; details of the procedure and results have been reported elsewhere (Zeltner et al. 2016). Items were constructed based on focus group results and the available literature (e.g. The DISABKIDS Group Europe 2006; Regnault et al. 2015).

This paper describes the second and third steps of the questionnaire's development for the patients' group aged from 8 to18 years. The second step was the exploration and adaptation of item comprehensibility and clarity ("cognitive debriefing") in children, adolescents, and adults. The third step was the psychometric evaluation of the instrument in a larger group. Item descriptives (e.g. mean, missing values, selectivity) served to select the most useful items, internal consistency of the questionnaire was calculated to assess reliability, and correlations between scores of the new instrument and those of well-established generic HrQoL questionnaires were used to test for convergent validity.

Methods

Subject Recruitment

For the cognitive debriefing, healthy children and adolescents as well as paediatric patients with UCD, OAs, or maple syrup urine disease (MSUD) from 8 to18 years were

recruited in Innsbruck and Zurich to test the comprehensibility and feasibility of the questionnaire booklet. Patients who had received a liver transplant for treatment of their metabolic disease were asked to recall the period before transplantation.

For psychometric evaluation, a sample of families with at least one child diagnosed with UCD or OA aged 8–18 years from the metabolic centres of Düsseldorf, Hamburg, Heidelberg, Innsbruck, and Zurich was invited by a member of the local medical team to participate in the study. Transplanted patients were not included.

For both study phases (cognitive debriefing and psychometric evaluation), individuals were excluded if they had insufficient command of the German language or were incapable of answering the questions due to neurocognitive constraints.

Materials

Questionnaire booklets were created for patients and parents. Patient self-report questionnaire booklets and parent proxy-report questionnaire booklets both contained basic demographic items, the newly developed questions for the MetabQoL 1.0 instrument, and well-established HrQoL questionnaires (described below). Parents worked on the booklet independently, while patients answered all questions in a one-to-one interview with a trained interviewer with medical or psychological background at their homes or at the hospital.

MetabQoL 1.0

Patient and parent questionnaires included the set of newly developed items for the MetabQoL 1.0 instrument. The items were elaborated by discussion among four of the authors (N.A.Z., M.L., M.B., M.H.); they were originally written in German and were translated into English for presentation in this report.

A set of 52 questions was developed for parallel self- and proxy assessment for patients from 8 to 18 years. Fifty questions are answered using 5-point Likert frequency scales (options: never, seldom, sometimes, often, always), with an additional answer option (e.g. “no problem with this”) for questions not applicable for all patients (e.g. tube feeding). Two questions assess disease severity during the last 12 months: (1) the disease has been “not bad at all,” “slightly bad,” “medium bad,” “bad,” or “very bad” and (2) number of hospital admissions “never,” “once,” “twice,” “three to five times,” or “six times or more.” Item scores can be aggregated to scale scores, which represent the core dimensions of physical, mental, and social HrQoL and a HrQoL total score.

PedsQL and DISABKIDS

Patients’ generic and chronic-generic HrQoL was assessed using self- and proxy assessment versions of the PedsQL (Varni et al. 1999; Felder-Puig et al. 2004) and the DISABKIDS-37 (The DISABKIDS Group Europe 2006); both instruments are reliable in terms of psychometric properties.

The PedsQL is a well-established instrument to assess the generic HrQoL of children and adolescents from 8 to18 years with a recall period of 4 weeks. Twenty-three items are answered on a 5-point Likert frequency scale. The PedsQL has scale scores for physical, social, emotional, and school-related HrQoL. Social, emotional, and school-related HrQoL can be aggregated to a psychosocial health score. Sum scores of all scales represent the HrQoL total score (Varni et al. 1999). The internal consistency of the PedsQL total scale scores in the current sample was good to excellent, with Cronbach’s $\alpha = 0.88/0.93$ (self-/proxy report).

The DISABKIDS assesses HrQoL in children with chronic disease from 8 to 16 years with a recall period of 4 weeks. The answering format comprises 5-point Likert frequency scales. Six scales represent the three main dimensions of HrQoL: limitation and medication (physical HrQoL), independence and emotion (mental HrQoL), and inclusion and exclusion (social HrQoL). Furthermore, a total HrQoL score can be computed including all scales (The DISABKIDS Group Europe 2006). The internal consistency of the DISABKIDS total scale scores in the current sample was good to excellent, with Cronbach’s $\alpha = 0.87/0.95$ (DISABKIDS self-/proxy report).

Cognitive Debriefing

The MetabQoL 1.0 questionnaire was tested for comprehensibility, relevance, and feasibility in a sample of five patients ($n = 2$ females, $n = 3$ males; age range = 8.72–16.77 years, mean = 12.42 ± 4.05 years; $n = 1$ liver transplanted) and their parents ($n = 5$ mothers). After completing the questionnaire, one-to-one interviews were conducted at the patient’s home, at the hospital, or by phone. The feasibility of the whole booklet for psychometric evaluation containing all three HrQoL questionnaires (MetabQoL 1.0, PedsQL, DISABKIDS) was assessed by interviewing four healthy partic-

ipants ($n = 2$ females, $n = 2$ males; age range = 9.83–18.09 years, mean = 12.66 ± 4.36 years) at home. All comments were discussed, and two of the authors (N.A.Z., M.H.) decided adaptations to the booklet.

Psychometric Evaluation

Cases were excluded if ≥20% of the MetabQoL 1.0 data were missing. The randomness of the remaining missing data was analysed with Little's MCAR test to ensure that the imputation method was appropriate. Missing values in the MetabQoL 1.0 were then imputed using the full information maximum likelihood (FIML) method (Arbuckle 1996).

The PedsQL and the DISABKIDS were scored according to the corresponding manuals (Varni et al. 1999; The DISABKIDS Group Europe 2006). Original scores of the MetabQoL 1.0 (never/not applicable =0, seldom =1, sometimes =2, often =3, always =4) were rescaled to values between 0 and 100 (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Values of positively formulated items were reversed to allow comparability with PedsQL and DISABKIDS. Accordingly, the best HrQoL was indicated by values of 100, worst by 0. Scales of physical, mental, and social HrQoL were computed by the mean of the corresponding item values. A total score was computed by the mean of all item values of the physical, mental, and social scales.

Item selection was performed in two steps. The first step was based on cut-offs derived from the literature (Bühner 2011) and the distribution of item descriptives in the current sample. Items were considered for exclusion if their mean value was ≥90/85 (self-/proxy report), or if selectivity was <0.3, or if correlation with other items was ≥0.80, or missing raw data was >5% (e.g., indicating low acceptance of an item), or if lack of comprehensibility had been documented in the interview setting.

The second selection step consisted of screening these problematic items. Items remained in the instrument if their content was vital to cover main issues from the focus groups, or in the interest of parallel content and comparability of the self- and proxy-report questionnaires.

Reliability defined as internal consistency for total and scale scores was determined using Cronbach's alpha. Scores ≥0.7 were considered acceptable (Scientific Advisory Committee of the Medical Outcomes Trust 2002). Concurrent validity between MetabQoL 1.0 and PedsQL/DISABKIDS subscales and total scores was determined by Spearman correlations. Due to the small sample size, factor analysis models were not applicable (Bühner 2011).

Analyses were performed with the statistical software package SPSS, version 22.0, and Amos Version 23.0 for Windows (IBM Corp. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp). A predefined significance level of $p < 0.05$ was set for all tests.

Results

Sample Characteristics

Of 87 families approached, 46 (53%) participated in the psychometric evaluation. This resulted in a sample of 80 participants: 38 patients ($n = 17$ females, $n = 21$ males; age range = 7.86–17.77 years, mean age = 12.56 ± 3.03 years; $n = 25$ OA, $n = 13$ UCD) with IT-IEM and 42 parents ($n = 35$ mothers, $n = 7$ fathers) of children with IT-IEM ($n = 19$ females, $n = 23$ males; age range = 8.49–18.34 years, mean age = 13.42 ± 3.04 years; $n = 27$ OA, $n = 15$ UCD; 32 parent-child pairs).

Cognitive Debriefing Results

Overall, patients and parents reported good feasibility of the MetabQoL 1.0 and the validation booklet. The majority of the questions were considered comprehensive and relevant to patients and parents. The guidance of the interviewer was important to improve patients' concentration and ensure that they understood the questions. Some questions (e.g., addressing motoric function, tube feeding) were not applicable for all patients, but their parents were aware of their relevance for other patients. Five questions had to be rephrased to increase comprehensibility and one to increase relevance.

Psychometric Evaluation Results

The self- and proxy questionnaires showed 6.01%/1.31% of randomly missing data in the MetabQoL 1.0 (Little's MCAR test, $x^2 = 10.02/x^2 = 464.94$, DF = 292/DF = 492, $p = 1.00/p = 0.80$) and therefore are qualified for the application of data imputation.

Item Selection

The item selection process resulted in a final sample of 28 items. Selected items and their scale affiliation, representing the first version of the MetabQoL 1.0, are listed in Table 1. Detailed item descriptives and the selection process of all items are shown in Supplementary Table 1.

Reliability

Psychometric properties of the MetabQoL 1.0 scales and their correlations are summarised in Tables 2 and 3. Means and skewness were higher for self-reported HrQoL than for

Table 1 Items included in the first version of the MetabQoL 1.0 for self-assessment[a]

	Items included based on item analysis[b]	Scale
1	Does it bother you that you are not allowed to eat anything you want?	Physical
2	Does it bother you that you have to eat even when you are not hungry?	Physical
3	Does it bother you that you have to take medications?	Physical
4	Does the taste of your medications bother you?	Physical
5	Does it bother you that you have regular check-ups?	Physical
6	Are you afraid of having blood taken?	Physical
7	Do you worry that you may have to go to the hospital due to an emergency?	Physical
8	Do you worry about the results of your blood test?	Physical
9	Does your metabolic disorder bother you when you are playing or during other activities?	Physical
10	Does it bother you that you cannot move as well as others?	Physical
11	Does it bother you that you get tired quickly?	Physical
12	Does it bother you that you often feel sick to your stomach?	Physical
13	Does it bother you that you have a feeding tube?	Physical
14	Do you have trouble keeping up in school/in your apprenticeship because of your metabolic disorder?	Mental
15	Are you happy?	Mental
16	Are you worried about your metabolic disorder?	Mental
17	Are you sad because you have a metabolic disorder?	Mental
18	Are you angry at having a metabolic disorder?	Mental
19	Are you afraid of the future because of your metabolic disorder?	Mental
20	Are you having problems doing things with friends because of your metabolic disorder?	Social
21	Are others less willing to be friends with you because of your metabolic disorder?	Social
22	Does it bother you that your parents or others in your family are particularly worried about you because of the metabolic disorder?	Social
23	Does it bother you that people treat you differently because of your metabolic disorder?	Social
24	Does it bother you that many people do not understand your metabolic disorder?	Social
25	Do you get left out because of your metabolic disorder?	Social
26	Does it bother you when other people feel sorry for you?	Social
27	How bad were your problems with your metabolic disorder over the last 12 months?	Severity
28	In the past 12 months, how often did you have to be admitted to the hospital in an emergency?	Severity

[a] The proxy assessment questionnaire consists of parallel rephrased items (e.g. item 1: Does it bother your child that he/she is not allowed to eat anything he/she wants?)

[b] Answering options: never, seldom, sometimes, often, always (items 1–26); not bad at all, slightly bad, medium bad, bad, very bad (item 27); never, once, twice, three to five times, six times or more (item 28)

proxy-reported HrQoL. Floor effects were not present, in contrast to ceiling effects, which were more dominant in self-reports than in proxy reports. Overall, reliability in terms of internal consistency was acceptable to excellent throughout all scales and total scores with a range of Cronbach's $\alpha = 0.70–0.93$, which was generally higher in proxy reports than in self-reports. All scale intercorrelations of the MetabQoL 1.0 were significant, ranging $r = 0.60–0.96$.

Validity

Convergent validity between the MetabQoL 1.0 and PedsQL/DISABKIDS was present and generally higher for the DISABKIDS than for the PedsQL (Table 4). Correlations were not limited to corresponding scales but also present between noncorresponding scales (e.g. MetabQoL 1.0 physical scale with PedsQL scales).

Discussion

This study presents the development process of the first disease-specific HrQoL questionnaire for paediatric patients with IT-IEM, the MetabQoL 1.0. The content validity of the questionnaire in general was ensured by involving patients and their parents in focus group interviews at the very beginning of the questionnaire development process (Zeltner et al. 2016). Questions for self- and proxy assessment were constructed based on statements from the focus groups. Cognitive debriefing was performed to further refine and focus the items of the questionnaire and to gain a first impression concerning the practical applicability of the instrument. Testing of the questionnaire in a larger sample of IT-IEM patients was conducted to analyse its psychometric properties.

Reliability in terms of internal consistency was acceptable to excellent for all scales and total scores. A general tendency towards high HrQoL was observed. This is consistent with data from other disease-specific questionnaires (Regnault et al. 2015; Bullinger et al. 2015). Correlation with the PedsQL and DISABKIDS scales was investigated to examine concurrent validity. Correlations in a medium range indicated that beyond measuring the construct of HrQoL in general, the MetabQoL 1.0 – as intended – adds specific content and information. This result underscores the benefit of this disease-specific questionnaire. As expected, correlations with the chronic-generic instrument, DISABKIDS, were higher than with the generic instrument, PedsQL. Since the DISABKIDS specifically addresses a population with health conditions, conceptualization of HrQoL was closer to the MetabQoL 1.0. Nevertheless, due to its more specific content, we

Table 2 Psychometric properties of the MetabQoL 1.0 questionnaire

Scale	Descriptive statistics							Reliability Cronbach's α
	N items	Mean	SD	Median	Skewness	% Floor	% Ceiling	
		Self/proxy	Self/proxy	Self/proxy	Self/proxy	Self/proxy	Self/proxy	Self/proxy
Physical	13	81.68/69.92	14.70/20.75	84.16/71.15	−0.92/−0.78	0/0	13.2/2.4	0.77/0.90
Mental	6	85.42/71.63	15.43/20.58	89.58/77.08	−1.36/−0.27	0/0	23.7/9.5	0.70/0.81
Social	7	86.47/72.87	15.60/20.22	92.86/73.21	−1.19/−0.36	0/0	26.3/14.3	0.70/0.81
Total score	**26**	**83.83/71.11**	**13.39/18.68**	**87.98/71.15**	**−0.95/−0.32**	**0/0**	**5.3/2.4**	**0.88/0.93**
Disease severity	2	81.25/75.30	21.89/26.69	87.50/87.50	−1.34/−1.12	0/0	39.5/31	

Table 3 Scale intercorrelations of the MetabQoL 1.0

Scales	Correlation coefficient
	Self/proxy
Physical – mental	0.67*/0.75*
Mental – social	0.60*/0.77*
Social – physical	0.66*/0.77*
Total score – physical	0.96*/0.95*
Total score – mental	0.78*/0.86*
Total score – social	0.79*/0.90*
Severity – physical	0.53*/0.57*
Severity – mental	0.48 */0.41*
Severity – social	0.48*/0.55*
Severity – total score	0.55*/0.57*

*$p < 0.05$

hypothesise that the MetabQoL 1.0 will be more responsive to disease-related changes than the chronic-generic DISABKIDS (Wiebe et al. 2003) and thus most valuable for clinical practice and research settings. This hypothesis will be followed up in long-term studies.

Generally, the results of proxy assessment were more favourable in terms of psychometric validity than the results of self-assessment. Self-assessment revealed higher means, increased skewness, lower reliability scores, and considerable ceiling effects for the mental and social scales. The modality of data collection may have influenced the answers; parents completed the questionnaires independently, while children were interviewed. The focus groups performed at the beginning of the questionnaire's development allowed space to freely express and discuss opinions and feelings, encouraged by exchange with other affected patients. The standardised questionnaire interview is a less open communication situation and may have favoured socially desirable answers. This idea is supported by the observation that in contrast to focus group interviews, where stigmatisation was a central topic (Zeltner et al. 2016), patients neglected this issue in the individual interview situation.

Higher self-ratings than proxy ratings of children's HrQoL in healthcare are well known from the literature (Eiser and Jenney 2007; Jamiolkowski et al. 2016). Children have a more intuitive, spontaneous view of a situation than adults and a tendency towards extreme answers (Chambers 2002). Furthermore, the effects of fatigue may be more prominent in children and adolescents than in adults and may have led to a lack of concentration during the interviews. This assumption is supported by the results of the cognitive debriefing, which emphasised the necessity of an interviewer guiding the patients through the questionnaire booklet to maintain concentration. Some IT-IEM patients have neurocognitive deficits, and their chronological age may not fully reflect their development age and concentration abilities. To reduce this bias, the questionnaire was kept as short as possible, with 28 items after psychometric evaluation. Furthermore, the more comprehensible 10-item smiley version of the MetabQoL 1.0 instrument for patients younger than 8 years, which is currently under development, may also prove useful in older patients with cognitive impairment.

Notably, 83% of the participating parents were female. In research about paediatric patients, higher representation of mothers compared to fathers is a well-known phenomenon (Goldstein et al. 2013) and may limit the generalisability of parent reports.

The pattern of correlation between the MetabQoL 1.0 scales and the PedsQL and DISABKIDS scales showed not only correlations between corresponding scales of the three instruments but also correlations between noncorresponding scales. Furthermore, correlations were observed between total score and physical, mental, and social scales of the MetabQoL 1.0. Highest correlations were found between physical HrQoL and the total score, which is, however, partly due to the large number of items these scores share. Overall, these findings lead to the hypothesis that there may be only a single dimension behind the items of the MetabQoL 1.0. The concept of the classical three

Table 4 Correlation coefficients between the MetabQoL 1.0 and the PedsQL (generic)/DISABKIDS (chronic generic)

		PedsQL						DISABKIDS						
								Physical		Mental		Social		
		Physical	Emotional	Social	School	Psychosocial	Total	Limitation	Medication	Independence	Emotion	Inclusion	Exclusion	Total
MetabQoL 1.0 self-report[a]	Physical	0.36*	0.43*	0.44*	0.41*	0.57*	0.52*	0.59*	0.57*	0.57*	0.55*	0.41*	0.47*	0.70*
	Mental	0.20	0.34*	0.23	0.43*	0.47*	0.36*	0.50*	0.57*	0.57*	0.69*	0.41*	0.53*	0.69*
	Social	0.33*	*0.47	0.28	0.26	0.42*	0.40*	0.53*	0.47*	0.53*	0.56*	0.27	0.43*	0.57*
	Total	0.37*	0.46*	0.45*	0.41*	0.57*	0.52*	0.63*	0.64*	0.63*	0.61*	0.43*	0.52*	0.75*
MetabQoL 1.0 proxy report	Physical	0.62*	0.51*	0.63*	0.52*	0.69*	0.72*	0.84*	0.62*	0.65*	0.67*	0.57*	0.74*	0.79*
	Mental	0.45*	0.60*	0.59*	0.47*	0.67*	0.62*	0.68*	0.79*	0.58*	0.86*	0.52*	0.86*	0.84*
	Social	0.67*	0.61*	0.72*	0.46*	0.73*	0.75*	0.82*	0.57*	0.73*	0.71*	0.70*	0.76*	0.85*
	Total	0.63*	0.59*	0.71*	0.53*	0.75*	0.75*	0.86*	0.72*	0.71*	0.78*	0.65*	0.83*	0.89*

* $p < 0.05$

[a] Sample size for convergent validity analysis was $n = 37$ in self-report ($n = 1$ excluded due to complete missing of DISABKDIS and PedsQL scores) and thereby different from all other psychometric analyses

dimensions of HrQoL is under discussion, and others have proposed the sole use of a single total HrQoL score (Solans et al. 2008). Particularly, in IT-IEM, the influence of the disease on patients' lives may be global. Physical aspects such as diet have a strong influence on social and mental aspects (feeling different or socially excluded). IT-IEM predominantly affect the brain. Therefore, cognitive functioning is strongly associated with the physical dimension. This association seems specific and is not present in the majority of generic HrQoL questionnaires for children (Rajmil et al. 2004) in which cognitive and emotional functioning constitutes an independent mental dimension.

Factor analysis, which might have elucidated the structure of the MetabQoL 1.0 in more detail, could not be performed due to the sample size (MacCallum et al. 1999). Although the international character of this study increased sample size, the diseases are rare, and large patient samples can only be gathered over time. Therefore, the questionnaire will be translated to be applied in larger samples in the near future. Further psychometric exploration will also include analyses of criterion validity, which was not addressed in this study. Criterion validity refers to the ability of a questionnaire to distinguish between different groups of patients. Furthermore, a larger sample may allow providing normative data. Normative data form the basis to compare between patients and to describe an individual's position within the reference group, which clearly is of long-term scientific interest. For now, the MetabQoL 1.0 is a tool to identify profiles of concerns and strains an individual patient experiences and opens the field for targeted clinical counselling. Furthermore, changes of a patient's HrQoL over time or under different treatment conditions can be monitored. These uses are not bound to normative data.

The MetabQoL 1.0 may be applied in clinical practice as well as in research, especially to detect changes in HrQoL over time. In clinical practice, monitoring HrQoL over time facilitates the identification of patients' needs and emotional and social aspects of the disease, which may not easily be detected in clinical routine. Notably, impaired social HrQoL has been shown for IT-IEM before (Fabre et al. 2013). Interestingly, the use of HrQoL instruments generally improves communication between patients and the medical team, which results in enhanced patients' well-being (Velikova et al. 2004). This is of particular importance during transitional phases such as transition to kindergarten, to school, and to adolescence (Packman et al. 2012; Khangura et al. 2015), when the impact of the disease and specific needs may change.

Considering research, disease-specific HrQoL measures are a most interesting additional approach for measuring outcome in clinical trials (Wiebe et al. 2003). The MetabQoL 1.0 is a promising tool for assessing disease-related HrQoL changes in IT-IEM. Furthermore, the questionnaire facilitates the exploration of predictors of HrQoL in IT-IEM patients and the development of interventions targeting patients' needs.

Conclusion

The MetabQoL 1.0 is the first psychometrically evaluated HrQoL questionnaire addressing the specific impact of IT-IEM on patients. Its targeted approach – in contrast to

generic measures – renders the MetabQoL 1.0 a valuable measure in clinical and research settings. Translation into other languages and further evaluation will allow broader application of the instrument.

Intellectual Property and Conditions of Use

Researchers or clinicians interested in using the MetabQoL 1.0© may contact the corresponding author (martina.huemer@kispi.uzh.ch).

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One Sentence Take-Home Message

A newly developed disease-specific health-related quality of life questionnaire for intoxication-type inborn errors of metabolism (MetabQoL 1.0) allows insight into the subjective burden of disease among children and adolescents.

Details of the Contributions of Individual Authors

N.A.Z. was involved in designing the study, collected and analysed the data, and drafted the manuscript. M.R.B. was involved in designing the study, contributed patient data, and critically reviewed the manuscript. A.B., R.E., D.K., S.K, C.M., S.S.B., and E.T. contributed patient data. J.Q. was involved in study design and gave advice on data analysis. P.B. was involved in coordination of the study and contributed patient data. M.A.L. was involved in designing the study, gave advice on data collection and analysis, and critically reviewed the manuscript. M.H. provided the original concept of the study, coordinated the study, and revised the manuscript. All authors read and approved the final version of the manuscript.

Conflict of Interest

Nina A. Zeltner and Martina Huemer have received research grants from Milupa Metabolics. Matthias R. Baumgartner, Aljona Bondarenko, Regina Ensenauer, Daniela Karall, Stefan Kölker, Chris Mühlhausen, Sabine Scholl-Bürgi, Eva Thimm, Julia Quitmann, Peter Burgard, and Markus A. Landolt declare no conflict of interest.

References

Arbuckle JL (1996) Full information estimation in the presence of incomplete data. In: Marcoulides GA, Schumacker RE (eds) Advanced structural equation modeling: issues and techniques. Lawrence Erlbaum Associates, Mahwah, NJ

Bühner M (2011) Einführung in die Test- und Fragebogenkonstruktion, 3rd edn. Pearson, Hallbergmoos

Bullinger M, Sommer R, Pleil A et al (2015) Evaluation of the American-English quality of life in short stature youth (QoLISSY) questionnaire in the United States. Health Qual Life Outcomes 13:43. doi:10.1186/s12955-015-0236-2

Chambers CT (2002) Developmental differences in Children's use of rating scales. J Pediatr Psychol 27:27–36. doi:10.1093/jpepsy/27.1.27

Dionisi-Vici C, Rizzo C, Burlina AB et al (2002) Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. J Pediatr 140:321–327. doi:10.1067/mpd.2002.122394

Eiser C, Jenney M (2007) Measuring quality of life. Arch Dis Child 92:348–350. doi:10.1136/adc.2005.086405

Fabre A, Baumstarck K, Cano A et al (2013) Assessment of quality of life of the children and parents affected by inborn errors of metabolism with restricted diet: preliminary results of a cross-sectional study. Health Qual Life Outcomes 11:158. doi:10.1186/1477-7525-11-158

Felder-Puig R, Frey E, Proksch K et al (2004) Validation of the German version of the pediatric quality of life inventory (PedsQL) in childhood cancer patients off treatment and children with epilepsy. Qual Life Res 13:223–234

Goldstein H, Akre C, Belanger RE, Suris JC (2013) Detached, distraught or discerning? Fathers of adolescents with chronic illness: a review of the literature. Int J Adolesc Med Health 25:109–117

Jamiolkowski D, Kölker S, Glahn EM et al (2016) Behavioural and emotional problems, intellectual impairment and health-related quality of life in patients with organic acidurias and urea cycle disorders. J Inherit Metab Dis 39:231–241. doi:10.1007/s10545-015-9887-8

Khangura SD, Tingley K, Chakraborty P et al (2015) Child and family experiences with inborn errors of metabolism: a qualitative interview study with representatives of patient groups. J Inherit Metab Dis. doi:10.1007/s10545-015-9881-1

Kölker S, Garcia-Cazorla A, Cazorla AG et al (2015a) The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1: the initial presentation. J Inherit Metab Dis 38:1041–1057. doi:10.1007/s10545-015-9839-3

Kölker S, Valayannopoulos V, Burlina AB et al (2015b) The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: the evolving clinical phenotype. J Inherit Metab Dis 38:1059–1074. doi:10.1007/s10545-015-9840-x

MacCallum RC, Widaman KF, Zhang S, Hong S (1999) Sample size in factor analysis. Psychol Methods 4:84–99. doi:10.1037/1082-989X.4.1.84

Matza LS, Patrick DL, Riley AW et al (2013) Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health

16:461–479. doi:10.1016/j.jval.2013.04.004 S1098-3015(13)01801-9 [pii]

Matza LS, Swensen AR, Flood EM et al (2004) Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health 7:79–92. doi:10.1111/j.1524-4733.2004.71273.x

Packman W, Mehta I, Rafie S et al (2012) Young adults with MSUD and their transition to adulthood: psychosocial issues. J Genet Couns 21:692–703. doi:10.1007/s10897-012-9490-1

Rajmil L, Herdman M, Fernandez de Sanmamed M et al (2004) Generic health-related quality of life instruments in children and adolescents: a qualitative analysis of content. J Adolesc Health 34:37–45. doi:10.1016/S1054-139X(03)00249-0

Regnault A, Burlina A, Cunningham A et al (2015) Development and psychometric validation of measures to assess the impact of phenylketonuria and its dietary treatment on patients' and parents' quality of life: the phenylketonuria – quality of life (PKU-QOL) questionnaires. Orphanet J Rare Dis 10:59. doi:10.1186/s13023-015-0261-610.1186/s13023-015-0261-6. [pii]

Scientific Advisory Committee of the Medical Outcomes Trust (2002) Assessing health status and quality-of-life instruments: attributes and review criteria on JSTOR. Qual Life Res 193–205

Solans M, Pane S, Estrada M-D et al (2008) Health-related quality of life measurement in children and adolescents: a systematic review of generic and disease-specific instruments. Value Health 11:742–764. doi:10.1111/j.1524-4733.2007.00293.x

Summar ML, Koelker S, Freedenberg D et al (2014) The incidence of urea cycle disorders. Mol Genet Metab 110:179–180. doi:10.1016/j.ymgme.2013.07.008

The DISABKIDS Group Europe (2006) The DISABKIDS questionnaires. Quality of life questionnaires for children with chronic conditions. Pabst Science Publishers, Lengerich, Germany

Upton P, Lawford J, Eiser C (2008) Parent-child agreement across child health-related quality of life instruments: a review of the literature. Qual Life Res 17:895–913. doi:10.1007/s11136-008-9350-5

Varni JW, Seid M, Rode CA (1999) The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 37:126–139. doi:10.1097/00005650-199902000-00003

Velikova G, Booth L, Smith AB et al (2004) Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol 22:714–724. doi:10.1200/JCO.2004.06.078

Waisbren SE, Gropman AL, Batshaw ML (2016) Improving long term outcomes in urea cycle disorders-report from the urea cycle disorders consortium. J Inherit Metab Dis 39:573–584. doi:10.1007/s10545-016-9942-0

Wiebe S, Guyatt G, Weaver B et al (2003) Comparative responsiveness of generic and specific quality-of-life instruments. J Clin Epidemiol 56:52–60. doi:10.1016/S0895-4356(02)00537-1

Zeltner NA, Landolt MA, Baumgartner MR et al (2016) Living with intoxication-type inborn errors of metabolism: a qualitative analysis of interviews with paediatric patients and their parents. JIMD Rep. doi: 10.1007/8904_2016_545

Zeltner NA, Huemer M, Baumgartner MR, Landolt MA (2014) Quality of life, psychological adjustment, and adaptive functioning of patients with intoxication-type inborn errors of metabolism – a systematic review. Orphanet J Rare Dis 9:159. doi: 10.1186/s13023-014-0159-8