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The impact of disease severity on the psychological well-being of youth affected by an inborn error of metabolism and their families: A one-year longitudinal study

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ABSTRACT

Background:

Inborn errors of metabolism (IEMs) refer to rare heterogeneous genetic disorders with various clinical manifestations that can cause serious physical and psychological sequelae. Results of previous studies on the impact of an IEM on health-related quality of life (HR-QoL) were incongruent and only few studies considered more broadly the psychological well-being of children with IEM and their families. Our objectives were to examine: (1) the impact of the IEM severity on the HR-QoL and psychological functioning of patients and their parents at baseline; and (2) its evolution over time; and (3) the correlation between parental and children's perspectives.

Methods: The sample included 69 pediatric patients (mean age = 7.55 y, SD = 4.59) with evaluations at baseline and after one year. We collected data on HR-QoL, child mental health and emotional regulation as well as on parental mood and stress using different validated questionnaires. IEM severity was rated by a clinician through the biological subdomain of the pediatric INTERMED instrument.

Results: Two groups of patients based on IEM severity scores were created ($n = 31$ with low and $n = 38$ with moderate/high IEM severity). The two groups differed with respect to age, diet and supplement intake. IEM severity had an impact on HR-QoL and behavioral symptoms in children, as well as on HR-QoL and stress in parents. For patients with moderate/high IEM severity, child and parental HR-QoL improved after 1-year of follow-up. We did not observe any significant difference between evaluations by patients versus parents.

Conclusions: Our findings demonstrate that moderate/high IEM severity altered child and parental psychological well-being, but also revealed a significant improvement after one-year follow-up. This observation suggests that patients with a moderate/high IEM severity and their families benefit from the care of an interdisciplinary team including a child psychologist specialized in IEMs. Moreover, in patients with higher IEM severity there may also be more room for improvement compared to patients with low IEM severity. Future studies should focus on observations over a larger time span, particularly during adolescence, and should include objective measurements.

Abbreviations: CERQ, Cognitive Emotional Regulation Questionnaire; ER, Emotion Regulation; HADS, Hospital anxiety and depression scale; HR-QoL, Health-Related Quality of Life; IEM, Inborn Errors of Metabolism; PIP, Pediatric Inventory for Parents; PKU, Phenylketonuria; SD, Standard Deviation; SDQ, Strengths and Difficulties Questionnaire; SE, Standard Error..

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1. Introduction

Inborn errors of metabolism (IEMs) refer to a heterogeneous group of genetic disorders that result from diminished enzyme activity, lack of a transport molecule or cofactor in a metabolic pathway [1,2]. The estimated overall birth prevalence for IEMs is 50.9 per 100,000 live births [1]. An untreated IEM can cause serious physical (e.g., psychomotor retardation, movement disorders, motor and/or cognitive handicap) and/or psychological sequelae [3–5] that are often not reversible and can even be lethal. Reflecting the heterogeneity of the diseases, therapeutic and treatment approaches of patients are very variable, ranging from regular clinical controls, daily oral intake of a drug (e.g., biotinidase deficiency), weekly or biweekly infusions (e.g., lysosomal storage diseases) to more or less restrictive diets with constant nutritional monitoring (e.g., phenylketonuria; PKU).

For a holistic approach to IEM management, assessment of the psychosocial difficulties of patients and their families is required. In this perspective, the concept of health-related “quality of life” (HR-QoL) refers to individuals’ satisfaction with multiple facets of their life such as physical, cognitive, social and emotional aspects [6]. The existing evidence on the HR-QoL in pediatric patients with an IEM and their families is inconclusive. A systematic review of the literature including 11 studies found inconsistent results, with some studies reporting decreased HR-QoL, while others reported similar or even better HR-QoL compared to control groups [7]. Similarly, previous studies investigating the HR-QoL in patients with a specific IEM (PKU) are also inconclusive, with the majority showing a HR-QoL score within the normal range [6,8–11], and one cross-sectional study reporting reduced HR-QoL scores in affected patients [12]. Additionally, two previous studies on patients with other IEMs (intoxication-type IEMs and IEMs with restricted diet) that were not included in the mentioned systematic review, found lower overall HR-QoL scores in patients compared to healthy children or children with leukemia [13,14]. A study on children with organic acidurias and urea cycle disorders showed a decreased HR-QoL in the physical domain [15]. Differences in results are likely due to the heterogeneity of the clinical expressions of the different IEMs (e.g., life-threatening condition, restrictive diet, daily nutritional supplement intake). Interestingly, two cross-sectional studies [11,16] conducted on PKU patients and their parents as well as one study on IEM patients with a restricted diet and their parents [17] found overall normal HR-QoL scores in children, but a decreased HR-QoL in their parents. These findings highlight the importance of considering both, children’s and parents’ perspectives. In order to address the differences due to the heterogeneity of diseases in this group, research needs to rely on a common index allowing for comparisons between different IEMs. Additionally, existing studies focused essentially on HR-QoL, leaving unexamined important aspects of the psychological functioning of parents and children with an IEM. More specifically, these factors include, among others, stress caused by the disease (i.e., difficulties encountered in daily life), coping or emotional regulation strategies [18] as well as resulting mental health difficulties. To our knowledge, no study to date has examined whether HR-QoL and/or indices of psychological functioning of children with an IEM disease and their parents remain stable or show changes over time. Given that previous studies showed a difference between perspectives of parents and children on HR-QoL [17,19], it is also important to compare parental self-reports and reports on their children with children’s self-reports.

1.1. The current study

Given the limitations and partially inconsistent findings of previous studies, the current study adopts an integrative perspective on psychological well-being of children and adolescents affected by an IEM and their families. Moreover, to our knowledge, no prior study has examined IEM burden (or severity) and the longitudinal aspects of psychological well-being, particularly in a heterogeneous sample (classified as low or

moderate/high burden) and compared both children’s and parents’ perspectives. The objectives of this study were to examine: (1) the impact of the IEM burden (i.e., severity) on the HR-QoL and psychological functioning of children, adolescents and their parents at baseline; and (2) their evolution over time (1-year follow-up); and (3) the correlation between parents’ and children’s perspectives, as an exploratory analysis.

2. Methods

2.1. Procedure

The study is in accordance with the Helsinki Declaration [20] and was approved by the ethics committee of the Vaud canton (CER-VD 2017–01256).

At baseline (T1), a member of the research group informed all study participants (children and their parents) about the aims and procedures of the study and obtained an informed consent, either before or after their consultation at the Pediatric Metabolic Center of the Lausanne University Hospital. Participants were invited to fill out questionnaires individually using the REDCap® tool. At the follow-up after 12 months (T2), the same procedure was repeated. For time reasons, some participants got an invitation by email with a link allowing them to fill out questionnaires from home.

2.2. Participants

The sample was derived from the pediatric patients followed at the Pediatric Unit for Metabolic Diseases of the Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois, CHUV). Inclusion criteria were: (1) confirmed diagnosis of an IEM, (2) IEM diagnosis known for at least 6 months, and (3) sufficient French-speaking skills. A total of 72 patients participated in the first part of the study (T1) that was carried out between January and December 2018 (40.3% females, mean age = 7.9, SD = 4.8, age range 1–18 years). During the 12 months between T1 and T2 a multidisciplinary care at a tertiary center was offered to patients and their families, which included besides doctors and nurses, a dietician, a child psychologist and a social worker, all specialized in IEMs. This is the standard care offered to all IEM patients in our unit. No intervention was planned nor implemented for the purpose of this study. All participants followed the same care throughout the whole study. Eleven patients did not participate at the 1-year follow-up assessment between January and December 2019, resulting in a total sample of 61 patients at T2 (dropout rate of 15%).

Concerning participation of the parents of pediatric patients at T1, 89 parents filled out the questionnaire, resulting in information on 69 out of 72 pediatric patients. Both parents answered for 20 pediatric patients (Supplementary Table 1), whereas for the other 49 children only one parent filled out the questionnaire (38 mothers and 11 fathers). Moreover, 18 out of the 69 pediatric patients for which both parents participated, also filled-out the questionnaire. For the remaining 3 out of 72 pediatric patients, only children answered the questionnaires. Participating parents included 58 mothers (65%, Mean age = 38 years, SD = 5.5) and 31 fathers (35%, Mean age = 40 years, SD = 6.6). The final sample used for the present analyses consisted of 69 patients.

2.3. Measures

2.3.1. Dependent variables

A summary of the measures used to create the dependent variables is presented in Supplementary Table 2.

Health-related quality of life (HR-QoL). HR-QoL was assessed using an adaptation of the French version of the Phenylketonuria Quality of Life (PKU-HR-QoL) questionnaire (PKU-HR-QoL [6,21]). The PKU-HR-QoL is an instrument specifically designed to report the disease-specific HR-QoL. The questionnaire was specifically developed for

PKU patients and therefore captures important aspects related to PKU, such as dietary restrictions and supplement administration, which are similar to other metabolic diseases and that are not present in other HR-QoL measures [21]. Hence, in order to have a more accurate picture on the impact of IEM on children and parents' lives, we decided to use this questionnaire, rather than a general HR-QoL one. In this study, we used the parent (for children aged 0–18 years), child (9–11 years) and adolescent (12–18 years) versions of the questionnaire. Each version of the HR-QoL investigates questions in four domains with ratings ranging from poor to excellent: (1) child symptoms (HR-QoL symptoms; 11 items on aches, fatigue and anxiety); (2) impact of IEM (HR-QoL impact; 15 items on impact of the disease on practical, emotional, and social life); (3) dietary supplements (6 items on intake management and adherence to intake); and (4) diet (10 items on management and adherence to diet, temptations and impact of diet). Higher scores indicate more impact on HR-QoL. For the present study, we analyzed data for HR-QoL symptoms (Cronbach's $\alpha = 0.848$) and HR-QoL impact (Cronbach's $\alpha = 0.868$).

Child mental health. The Strengths and Difficulties Questionnaire (SDQ) was used to screen for emotional and behavioral symptoms in children and adolescents (French validation [22]). Each item is rated from 0 (not true) to 2 (very true). We computed scores for emotional (Cronbach's $\alpha = 0.725$) and behavioral (Cronbach's $\alpha = 0.790$) problems. Higher scores indicate more symptoms. We used the parent-completed version for children aged 2 to 17 years, as well as the self-reported version for adolescents aged 12 to 17 years.

Emotion regulation strategies. The Cognitive Emotional Regulation Questionnaire (CERQ) was used to assess the adaptive or nonadaptive emotion regulation strategies used following a negative life event. The questionnaire consists of 36 items, each self-rated on a scale ranging from 1 (almost never) to 5 (almost always). We used the adult self-report version for parents of pediatric patients (French validation [23]) and the adolescent self-report version for pediatric patients (French validation [24]). The CERQ questionnaire showed a Cronbach's α of 0.882 for adaptive and 0.847 for nonadaptive emotional regulation strategies.

Parental stress. Difficulties perceived by parents that were related to the chronic illness of their child were assessed with the Pediatric Inventory for Parents (PIP [25]). This parental self-administered questionnaire was used to assess areas of stress and worry in parents of children with an IEM. The PIP consists of 42 items, each rated on a frequency scale (ranging from 1 = never to 5 = very often), with higher scores corresponding to more difficulty. Cronbach's α for this instrument was 0.959.

Parental mood difficulties. We used the Hospital anxiety and depression scale (HADS; French validation [26]) to assess self-reported depressive and anxiety symptoms in parents. HADS is a 14-item self-report scale: 7 items for the anxiety subscale and 7 for the depression subscale. Each response is scored from 0 to 3, providing a quantitative assessment of the intensity of the symptom in the past week. The range of possible scores extends from 0 to 42, with high scores corresponding to the presence of acute symptomatology. Responses from our sample of parents yielded a Cronbach's α of 0.827 for the anxiety subscale and a Cronbach's α of 0.841 for the depression subscale.

2.3.2. Independent variables and covariates

Index of IEM severity. In order to have an index of the severity of the child's IEM, the same physician of the Pediatric Unit for metabolic diseases filled out the "Biological Domain" scale of the pediatric INTERMED tool [27,28] at baseline (T1). The single-rating approach allowed for consistency in the rating because of the extensive knowledge of the patients and their medical records by the physician, allowing for homogeneous scores. Additionally, the physician was blind with respect to the results of the questionnaires rated by the participants and their parents. The scale is composed of five subscales (i.e., chronicity, diagnostic dilemma, symptom severity / impairment, diagnostic / therapeutic challenge and complications & life threat), each rated in 4 points (range = 0–3) for a total IEM severity score ranging between 0 and 15,

with higher scores indicating more severe IEMs. Following the Kernel distribution of the IEM severity index scores in our sample, and the cutoff set by the authors of this tool at 1/3 of the total score for identification of case complexity [29], we categorized participants into one of the following categories: low (scores between 0 and 5; $n = 31$) or moderate/high IEM severity (scores between 6 and 15; $n = 38$). Cronbach's α for internal consistency of the index of IEM severity items yielded from our sample was 0.840.

Covariates. Information on socio-demographics (sex and age of the child, age at the diagnosis, parent's age, educational levels, occupation and marital status), diet, treatment, and supplement was collected through a standardized questionnaire. Diet was defined as patients following a specific dietary restriction. Treatment and supplement included all drugs and dietary supplements that children had to take for their IEM.

2.4. Data analyses

Both parents responded for 20 out of 69 pediatric patients at T1 and for 11 pediatric patients at T2. We assessed if parental responses differed between mothers and fathers and found a single significant difference for coping strategies at T1, with mothers self-reporting more adaptive coping strategies than fathers, $t(19) = 2.37, p = .029$. Accordingly, for pediatric patients for which both parents responded, we provided a mean score between maternal and paternal scores for each variable; for all other pediatric patients we used the score that either mothers or fathers provided. In order to test the heterogeneity of different types of IEM, we performed Kruskal-Wallis test to compare the outcome variables of interest (psychological well-being) between the five main IEM groups, including Biotinidase deficiency, BH4-responsive PKU, Classic PKU, MCADD, and other IEM types of disease. Since we did not find any statistical difference between the five groups with respect to psychological well-being (c.f. supplementary Table 4), except for HR-QoL symptoms and parental stress, we decided to lump together all types of IEM and assess their severity by using the pediatric INTERMED biological subdomain. This allowed us to keep the data of the whole sample (including other IEM types of disease) and to have a general overview of the impact of the IEM burden on the psychological well-being.

Patients age correlated significantly with the severity score ($r = 0.328, p = .005$). Moreover, taking into account a previous publication [13], data should be controlled for time since diagnosis and sex. Thus, to assess their impact on the IEM severity, we computed multiple analyses of variance (MANOVA) controlling for age, time since diagnosis and sex (MANCOVA) on psychological well-being. Likewise, repeated-measures ANOVA (RM-ANOVA) were computed to assess the impact of IEM severity and time (evolution over 1-year) on psychological well-being. Finally, we conducted exploratory analyses (Pearson correlational and paired-sample t -tests) to examine the relationships and differences between both perspectives (i.e., adolescents and their parents). Analyses were completed using SPSS version 26 for Windows (IBM Corp, NY, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Descriptive

The description of the sample used to investigate the impact of IEM severity on child and parental dimensions is presented in Table 1. Diagnostic characteristics of the sample can be found in the Supplementary Table 3. The majority of parents were either married or in a couple (73% married and 13% in couple), more than 80% had a post-compulsory school degree or higher and 77% of workers were either unqualified (25%) or qualified workers (52%). Regarding HR-QoL, rated by parents, 54% of parents from our sample indicated that their child showed no or little symptoms, with 39% reporting moderate symptoms and 7% reporting a major impact. Similarly, analyzing frequencies for

Table 1
Sample characteristics at baseline.

	Overall sample	Low severity	Moderate/high severity	low vs. moderate/high severity
	Mean (SD)	Mean (SD)	Mean (SD)	p-value ^a
	min-max	min-max	min-max	
	n = 69	n = 31	n = 38	
Children				
Sex, % (n)				
Females	39.13 (27)	45.16 (14)	34.21 (13)	0.354 ^b
Males	60.87 (42)	54.84 (17)	65.79 (25)	
Age (years)	7.55 (4.59)	5.79 (4.05)	9.00 (4.56)	0.003
	1–17	1–16	1–17	
Age at diagnosis (years)	1.65 (3.28)	0.55 (1.69)	2.61 (3.97)	0.007
	0–14.25	0–8.08	0–14.25	
Diet, % (n)	20.29 (14)	3.23 (1)	34.21 (13)	0.002 ^c
Treatment, % (n)	78.26 (54)	83.87 (26)	73.68 (28)	0.308 ^b
Supplement, % (n)	18.84 (13)	3.23 (1)	31.58 (12)	0.004 ^c
Severity	7.06 (3.73)			
	2–14			
Time since diagnosis (months)	74.43 (47.05)	66.94 (46.83)	80.89 (46.93)	0.229
	5–207	5–194	13–207	
HR-QoL symptoms	25.94 (15.52)	19.35 (12.71)	31.31 (15.67)	0.001
	1.14–75.00	1.14–50.00	1.14–75.00	
Emotional symptoms	4.21 (3.11)	3.72 (3.22)	4.54 (3.03)	0.312
	0–12	0–12	0–11	
Behavioral symptoms	6.14 (3.72)	4.50 (2.74)	7.24 (3.91)	0.004
	0–16	0–11	1–16	
Parent(s)				
Age	38.39 (5.55)	36.66 (4.62)	39.83 (5.89)	0.021
	25–53	31–53	25–51	
Education level, % (n)				
Compulsory school	18.46 (12)	20.69 (6)	16.67 (6)	0.884 ^b
Apprenticeship certificate	38.46 (25)	34.48 (10)	41.67 (15)	
Professional maturity Certificate	15.38 (10)	13.79 (4)	16.67 (6)	
University or higher education	27.69 (18)	31.03 (9)	25.00 (9)	
Occupation, % (n)				
Unqualified employee	24.59 (15)	27.59 (8)	21.88 (7)	0.787 ^c
Qualified employee	52.46 (32)	55.17 (16)	50.00 (16)	
Employed	11.48 (7)	6.90 (2)	15.63 (5)	
Liberal profession	11.48 (7)	10.34 (3)	12.50 (4)	
Marital status, % (n)				
Married	73.13 (49)	74.19 (23)	72.22 (26)	0.870 ^c
Divorced	8.96 (6)	6.45 (2)	11.11 (4)	
Single	4.48 (3)	3.23 (1)	5.56 (2)	
With a partner	13.43 (9)	16.13 (5)	11.11 (4)	
HR-QoL impact	26.47 (13.76)	21.46 (9.93)	30.56 (15.15)	0.004
	0.69–65.93	5.56–47.89	0.69–65.93	
Parental stress	81.76 (27.56)	70.02 (25.51)	91.59 (28.47)	<0.001
	36.50–167.00	39.00–151.50	36.50–167.00	
Anxiety symptoms	3.80 (3.80)	3.27 (3.43)	4.23 (4.07)	0.306
	0–20	0–12	0–20	
Depressive symptoms	6.49 (4.00)	5.47 (3.73)	7.32 (4.07)	0.058
	0–21	0–15.50	0.50–21	
Adaptive ER	12.87 (2.99)	12.92 (3.08)	12.83 (2.96)	0.898
	4.40–18.80	4.40–18.80	6.80–18.00	
Nonadaptive ER	6.93 (2.14)	6.84 (2.30)	7.01 (2.02)	0.748
	3.50–12.25	3.50–12.25	4.38–12.25	

Abbreviations: SD, standard deviation; HR-QoL, Health-Related Quality of Life; ER, emotion regulation.

^a Student's *t*-test.

^b Chi-square test.

^c Fisher's Exact test.

the impact of IEM on their own HR-QoL, results showed that 55% of parents reported no or very limited impact of the IEM, while 39% indicated a moderate impact and 6% indicated a major impact.

Regarding children's mental health rated by parents, results showed that 14.5% of parents indicated that their children presented emotional and/or behavioral symptoms, 14.5% presented a suspicion for such symptoms, and 71% of children did not present any symptom.

According to the clinical cutoff for anxiety and/or depression, 22% of parents reported mood symptoms.

Children with low versus children with moderate/high IEM severity differed with respect to the age of the children and of the parents, age at

diagnosis, diet, supplement, as well as HR-QoL symptoms and impact, behavioral symptoms and parental stress (Table 1).

3.2. Impact of disease burden at baseline and its evolution over time

Results on the impact of IEM severity on children's and parental dimensions are presented in Table 2.

When we examined the impact of IEM severity on children's and parental dimensions at baseline, we found that IEM severity had an influence on parental rated HR-QoL symptoms and impact, as well as on behavioral symptoms in children and parental stress. The parental-rated

Table 2
Impact of IEM severity on children’s and parental dimensions at baseline.

Dependent variables	IEM severity low vs. moderate/high at baseline			Baseline vs. follow-up p-values ^b		
	Estimate	SE	p-value ^a	IEM severity	Time	IEM x Time
Children						
HR-QoL Symptoms	12.47	4.24	0.005	<i>0.254</i>	0.048	0.042
Emotional symptoms	0.23	0.88	<i>0.797</i>	<i>0.836</i>	<i>0.948</i>	<i>0.904</i>
Behavioral symptoms	3.44	1.00	0.001	<i>0.097</i>	<i>0.449</i>	<i>0.086</i>
Parents						
HR-QoL impact	11.07	7.40	0.007	<i>0.513</i>	<i>0.127</i>	0.011
Parental stress	19.62	7.78	0.015	<i>0.086</i>	<i>0.147</i>	0.044
Anxiety symptoms	1.35	1.09	<i>0.219</i>	<i>0.475</i>	<i>0.187</i>	<i>0.151</i>
Depressive symptoms	2.36	1.19	<i>0.053</i>	<i>0.492</i>	<i>0.161</i>	0.042
Adaptive ER	-0.20	0.89	<i>0.821</i>	<i>0.361</i>	<i>0.793</i>	<i>0.784</i>
Nonadaptive ER	0.26	0.64	<i>0.681</i>	<i>0.599</i>	<i>0.668</i>	<i>0.103</i>

Abbreviations: IEM, Inborn Errors of Metabolism; SE, standard error; HR-QoL, Health-Related quality of life; ER, Emotion Regulation. Statistically significant results are in bold.

p-values are in italic.

^a p-value resulting from the multivariate analyses of variance controlling for age, sex and time since diagnosis.

^b p-value resulting from the repeated-measure analyses of variance controlling for age, sex and time since diagnosis.

dimensions were higher in the moderate/high severity group compared with the low severity group.

Additionally, we also investigated the impact of dietary treatment on children’s and parental dimensions at baseline. We did not find any significant impact on the different dimensions (*ps* > .05).

Results on the impact of IEM severity on children’s and parental dimensions after 1-year follow-up showed no main effects of IEM severity (low vs. moderate/high severity). However, we found a change of HR-QoL symptoms over time (*p* = .047). Results showed a time by IEM severity interaction on HR-QoL impact and symptoms, as well as on parental stress and depressive symptoms. In particular, post-hoc comparison indicated a significant decrease of HR-QoL impact in the moderate/high IEM severity group (*p* = .003), whereas no changes were observed in the low IEM severity group. Additionally, for HR-QoL symptoms parental stress and depression, the patterns were similar, but not statistically significant.

3.3. Exploratory analyses

3.3.1. Correlation between children’s and parental dimensions

Correlational analyses are reported in Table 3. Age and time since diagnosis did not correlate with parental dimensions. Children’s dimensions (HR-QoL symptoms as well as behavioral and emotional symptoms) correlated positively and significantly with parental dimensions (HR-QoL impact, parental stress, depression, anxiety symptoms and nonadaptive emotion regulation strategies).

3.3.2. Multiple perspectives

We computed correlations between parents’ and children’s ratings on HR-QoL symptoms and mental health of children, namely the dimensions that are rated from both perspectives (*n* = 18). We found a positive correlation between HR-QoL impact rated by children and by parents (*r* = 0.494, *p* < .05). Similarly, a positive correlation was found between the children’s and the parents’-rated versions of the adaptive

emotion regulation questionnaire (*r* = 0.638, *p* < .05). Moreover, pairwise comparisons of youth-report and parent-report on HR-QoL symptoms (*n* = 18), and on mental health (behavioral and emotional problems, *n* = 10) did not reveal any significant differences (results not shown).

4. Discussion

The present study examined the impact of IEM severity (burden) on psychological well-being at baseline and after a one-year follow-up in a sample of pediatric patients and their parents. As exploratory purpose, we also assessed the relationships and differences between multiple perspectives (adolescents and parents) on several psychological well-being measures. Results showed an impact of IEM severity on children and parents’ psychological well-being at baseline. In particular, the disease severity was found to have an impact on the HR-QoL of children and their parents, as well as on behavioral symptoms in children and parental stress. Additionally, our results indicated that in families with a child suffering from an IEM with a moderate/high severity, the HR-QoL improved at a 1-year follow-up, which might suggest a certain positive effect of the psychosocial services offered to patients and their families at our clinic.

Concerning the different dimensions that were measured in the present study, we found that the biggest impact of IEM severity was on HR-QoL of children and their parents, thus confirming results of previous studies [6,13,14]. Children’s and parental psychopathology, as well as parental emotional regulations were only slightly influenced by the disease severity. To our knowledge, no previous literature exists on this topic. Overall, these findings suggest focusing on HR-QoL as primary target for prevention and intervention in families with a child affected by an IEM. Moreover, children suffering from an IEM and their families should receive highly specialized interdisciplinary care at a tertiary center, including the involvement of a dietician, psychologist/psychiatrist and social worker experienced in IEMs in order to address the

Table 3
Correlational analyses between children’s and adolescents’ and parents’ dimensions.

Children / Parent	HR-QoL impact	Parental stress	Depressive symptoms	Anxiety symptoms	Adaptive ER	Nonadaptive ER
Age	0.100	0.238	0.106	0.039	0.016	-0.107
Time since diagnosis	0.122	0.194	0.125	0.021	0.056	-0.054
HR-QoL symptoms	0.592**	0.640**	0.621**	0.526**	0.086	0.344**
Behavioral symptoms	0.356**	0.341**	0.428**	0.258*	0.138	0.273*
Emotional symptoms	0.433**	0.575**	0.506**	0.398**	0.045	0.430**

Abbreviations: HR-QoL, Health-Related Quality of Life; ER, Emotion Regulation.

* *p*-value < .05; ** *p*-value < .01.

various aspects of family life that are affected by the diagnosis of an IEM.

Comparison of the two IEM severity groups showed considerable differences. Parents of children with moderate/high IEM severity reported significantly more behavioral problems and symptoms in their children, resulting in a lower HR-QoL compared to children with lower IEM severity. Since the perspective of children and their parents on their psychological well-being were consistent (exploratory analysis), one might hypothesize that children and adolescents with moderate/high IEM severity would report more frequently behavioral problems compared to children with low IEM severity. The finding of increased behavioral problems in children with higher IEM severity is in line with previous studies on the HR-QoL among IEM children [12,14].

Interestingly, in our sample, unlike behavioral problems, emotional problems were not reported more frequently by parents of children with moderate/high IEM severity than by parents of children with low IEM severity. Moreover, our results also showed that IEM severity does not have an impact on parental emotional problems (i.e., anxiety and depressive symptoms). These results suggest that IEM severity does not have an impact on emotional problems. A recent study found the subgroup of children with non-acute IEM to report more emotional problems compared to children with acute IEM [13], but in our sample, we did not find any differences between moderate/high versus low IEM severity groups. The different results could be due to methodological differences, specifically to the instruments used to assess both, HR-QoL and emotional problems. Moreover, we determined IEM severity groups using a questionnaire, rather than diagnostic groups as the sample analyzed by Bösch et al. [13]. Finally, the difference in findings may also be due to the different samples used. Whereas Bösch et al. [13] examined patients with intoxication-type IEM, we had a more heterogeneous sample. However, supplementary analyses showed that the different diagnostic groups did not differ with respect to psychological well-being, suggesting a quite homogenous sample.

Our findings also demonstrated that the psychological well-being of children with IEMs was not influenced by dietary treatment. This finding is in contradiction with a recent study that showed a negative impact of dietary treatment on HR-QoL of children with an intoxication-type IEM [13]. In our sample, it does not appear that dietary restrictions are a burden for children's HR-QoL. However, only few participants were under a strict diet (20.29%) and results could therefore lack of statistical power. Nevertheless, differences in findings could be due to methodological differences, such as the use of the instrument used to assess HR-QoL, as well as the different mean age of the two samples (7.9 vs 11.6). We might hypothesize that adolescents have a harder time following a strict diet than younger children mainly included in our sample.

Concerning parental dimensions, HR-QoL and stress were negatively affected by the severity of IEM in their children, whereas parental emotional regulations, as well as anxiety and depression symptomatology were not influenced by the burden of the disease. This finding is in contradiction with a previous study that found mothers of children with PKU had higher scores for depression and anxiety than parents of control children [30]. The different finding could be due to the design of the two studies. Indeed, Gunduz et al. [30] compared parents of IEM children to parents of control children, whereas we did not use a control group for comparison. Future studies should focus on other psychological measures and use the same study design in order to elucidate this aspect in more details. However, to our knowledge, no other study looked at the impact of IEM's severity on parental mental health. Future studies should focus on other psychological measures in order to elucidate this aspect in more details.

Although impact of IEM severity on psychological well-being did not change over time, we found a significant increase of HR-QoL in the moderate/high IEM severity group at the second time point. We could make the assumption that the higher the IEM severity, the greater the improvement will be. Indeed, previous studies have shown that the early detection of a disease predicts a better patient care, with reduced adverse events, and consequently a better outcome [31], compared to

less severe diseases. To our knowledge, our study is the first to examine HR-QoL changes over time in IEM patients and their families. Further studies should assess the impact of treatment on psychosocial functioning of patients with IEM and their families.

Strengths of this study are the novel approach adopted that uses an index for disease severity, as well as its longitudinal design. Relying on a well-validated tool [27], we circumvented the methodological difficulties related to the heterogeneity in the clinical expressions of the many existing IEMs by using a unique index of child IEM severity. This allowed us to examine a larger monocentric sample of IEM pediatric patients by accounting for the existing heterogeneity across different IEMs. Additionally, unlike previous studies, we used multiple measures to assess the psychological well-being of children, adolescents and their parents. Likewise, we employed both, the children's and the parental perspective for their psychological well-being assessment.

The different conclusions drawn from the findings reported in this study should be considered in the context of the limitations of our study: first, the size of the sample is relatively small and, most importantly, very heterogeneous in terms of different IEMs and their respective multiple clinical expressions. Although we found no major differences in different types of IEM with respect to psychological well-being, future studies should examine IEM types separately in order to understand whether there are differences. Second, besides the categorization by the severity index, the measures consisted of questionnaires that were mainly reported by the parent on their child. Future studies should also consider objective measures for HR-QoL and well-being, such as material resources (e.g., food, housing) and social attributes (e.g., health, education, social interactions) and should use data derived from official statistical collections [32]. Third, our follow-up measure was only a year later than the baseline measure. It is thus important that future studies examine stability of HR-QoL and predictors of HR-QoL over a larger time span, in particular during the adolescence period, which has been shown to be a critical period for compliance with treatment and strict diets [33]. Fourth, the pediatric INTERMED instrument used to assess IEM severity has only been validated among children with inflammatory bowel disease, but not among children with IEMs [34]. Fifth, we could not adjust for cognitive impairment in our analyses on the impact of IEM severity on behavioral problems, since we did not collect this information. Future studies should consider this potential confounder when examining the associations between IEM severity and behavioral problems in patients.

5. Conclusions

The results of this study showed an important impact of IEM severity on the psychological well-being of children and their families, particularly on their HR-QoL that improved after a one-year follow-up. These findings might suggest that children with an IEM, particularly those with moderate/high severity, and their families benefit from specialized care at a tertiary center with an interdisciplinary team experienced in IEM including a child psychologist, a social worker and a dietitian. Moreover, in patients with higher IEM severity there may also be more room for improvement compared to patients with low IEM severity. This approach seems to enhance coping with difficulties in their physical, cognitive, social and emotional well-being. Our results also demonstrate that the use of an instrument measuring disease severity allows the comparison of a heterogeneous patient group. Future studies should focus on the evaluation of HR-QoL over a larger time span and particularly during adolescence, ideally by using objective measurements.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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