



## Caregiver burden, and parents' perception of disease severity determine health-related quality of life in paediatric patients with intoxication-type inborn errors of metabolism

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### ABSTRACT

**Background:** Living with a non-acute (phenylketonuria) or acute (e.g. urea cycle disorders, organic acidurias) intoxication-type inborn error of metabolism (IT-IEM) can have a substantial impact on health-related quality of life (HrQoL) of paediatric patients and their families. Parents take primary responsibility for treatment monitoring and experience worry and fear about their child's health status. Quantitative evidence on parental psychological factors which may influence the HrQoL of patients with IT-IEM are sparse to non-existent.

**Methods:** In this multicenter survey study 50 parents of IT-IEM patients (ages 5–19) assessed the severity of their child's disease, reported on caregiver burden, and proxy-rated their child's HrQoL. Additionally, 35 patient self-reports on HrQoL were obtained ( $n = 16$  female patients,  $n = 19$  male patients). Multiple linear regressions were conducted to examine the predictive power of child age, sex, medical diagnosis type (acute / non-acute), parental perceived disease severity and caregiver burden on patients' HrQoL. Mediation analyses were used to investigate the relation of caregiver burden and parental ratings of disease severity with patients' HrQoL.

**Results:** Significant regression models for self-reported [ $F(5,34) = 10.752, p < .001, R^2 \text{ adj.} = 0.59$ ] and parent proxy reported HrQoL [ $F(5,49) = 20.513, p < .001, R^2 \text{ adj.} = 0.67$ ] emerged. High caregiver burden and perceived disease severity predicted significantly lower patient self- and proxy-reported HrQoL while type of diagnosis (acute versus non-acute) did not. Female sex predicted significantly lower self-reported HrQoL. High caregiver burden was the mediating factor between high perceived severity of the child's disease and lower proxy- by parent rated HrQoL.

**Conclusion:** Detecting elevated burden of care and providing support for parents seems crucial to prevent adverse consequences for their children's HrQoL. Intervention studies are needed, to assess which support programs are most efficient.

**Abbreviations:** OA, Organic acidurias; UCD, Urea cycle disorders; IT-IEM, Intoxication-type inborn errors of metabolism; PKU, Phenylketonuria; HrQoL, Health-related quality of life; CH, Switzerland; AT, Austria; DE, Germany; PA, Propionic academia; GA1, Glutaric aciduria type 1; IVA, Isovaleric acidemia; MMA, Methylmalonic aciduria; OTC, Ornithine transcarbamylase; ASS, Argininosuccinate synthase 1; CBT, Cognitive-behavioural therapy; PST, Problem-solving therapy.

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## 1. Introduction

Organic acidurias (OA), urea cycle disorders (UCD) and maple syrup urine disease are acute intoxication-type inborn errors of metabolism (IT-IEM). Patients live with a constant risk for metabolic crisis and neurological sequelae and often have to adhere to a protein-restricted diet. In contrast, phenylketonuria (PKU) is a non-acute IT-IEM without metabolic crises, but PKU-patients likewise adhere to a protein-restricted diet to prevent long-term cerebral damage caused by accumulating concentrations of plasma phenylalanine. In both acute and non-acute IT-IEM amino acid supplements and specific medication are common additions to the dietary treatment regimen. Previous research suggests that paediatric patients' and their parents' everyday life is significantly affected by the considerable disease and treatment burdens of IT-IEM.

In qualitative studies, patients with acute and non-acute IT-IEM reported multiple stressors of social (e.g. stigma due to dietary restrictions), emotional (sadness, shame, longing for cure), and disease-related (e.g. medical procedures) nature [1–3]. Recent quantitative approaches investigating patients' self and proxy reported health-related quality of life (HrQoL; the perception of the impact of disease and treatment on functioning in a variety of dimensions [4]) indicated impairments in several domains in patients with acute and non-acute IT-IEM [5,6]. Despite growing awareness of impaired HrQoL in paediatric IT-IEM, the knowledge about its determinants is limited.

Based on previous chronic-generic and condition-specific research, caregiver burden could be one of these determinants. This broad construct comprises responsibilities, stressors, and challenges that are associated with providing care for a child [7]. Parents play a critical role in their child's adjustment to a chronic illness and are highly involved in treatment management and disease monitoring beyond providing the "usual" parenting [8]. Caring for a child with IT-IEM goes along with additional psychosocial, organisational, and financial burdens for parents [1,9–11]. In other chronic paediatric conditions such as diabetes or epilepsy, parents reported a considerably high caregiver burden that was associated with behavioural, and disease-related sequelae and impaired HrQoL of their children [12–15]. Furthermore, the parent-reported assessment of the severity of their child's chronic disease is a risk factor for increased caregiver burden and consecutively for lower HrQoL of the patients [16–21].

So far, quantitative evidence relating caregiver burden and parental perceived disease severity to HrQoL of paediatric patients with acute and non-acute IT-IEM is scarce. Only by identifying meaningful risk factors, family-centered care and tailored interventions can be provided to improve patients' HrQoL in the long-term. This study investigates possible associations and mediating processes between caregiver burden, disease severity of the child as perceived by parents and patients' HrQoL under consideration of sociodemographic characteristics and medical diagnosis. We hypothesised that caregiver burden mediates perceived disease severity and patients' HrQoL.

The following research questions were investigated:

1. Does higher caregiver burden predict lower HrQoL of patients under consideration of sociodemographic variables (sex, age) and objective type of diagnosis (acute vs. non-acute)?
2. Does a higher perceived disease severity by parents predict lower HrQoL of patients under consideration of sociodemographic variables (sex, age) and medical type of diagnosis (acute vs. non-acute)?
3. Does parental stress mediate the relation between parental severity perception and patients' HrQoL?

## 2. Methods

### 2.1. Recruitment and data collection

The recruitment and data collection was conducted from December

2020 to December 2021. Patients between 7 and 18 years with an acute or non-acute IT-IEM diagnosis and parents of children with respective conditions (ages 5–19) were recruited by their metabolic physicians in five Swiss, German and Austrian metabolic centres (Zurich, CH; Bern, CH; Basel, CH; Innsbruck, AT; Freiburg, DE). An online survey was sent to 67 eligible families. From 50 families one parent form was completed (response rate = 75%). Of 42 patients fulfilling the inclusion criteria 35 participated (response rate = 83%). Beside sociodemographic data the survey comprised patient- and parent-reported outcome measures (see below: 2.2 - Questionnaires). Completing the survey approximately took parents 35 min, and patients 20 min. The specific IT-IEM diagnosis was assessed with an online survey completed by the responsible physicians who had no access to participants' questionnaire responses. The online surveys were conducted using the REDcap electronic data capture tools hosted at University Children's Hospital Zurich [22].

### 2.2. Questionnaires

Parent- and self-reported HrQoL was assessed with the German version of the MetabQoL [23], a questionnaire specifically developed for paediatric IT-IEM. Self-reports were collected from patients aged 7 years and older. The 28-item MetabQoL provides a total HrQoL score and encompasses physical (13 items), mental (6 items), and social (7 items) dimensions. Items are rated on a 5-point Likert scale and recoded into a scale from 0 to 100 with higher scores indicating better HrQoL.

An additional scale of the MetabQoL (2 items, recoded scores from 0 to 100) captures *perceived disease severity* with higher scores indicating a higher perceived disease severity.

*Caregiver burden* was measured with the German adaptation of the Impact-on-Family Scale [24] ("Familien-Belastungs-Fragebogen, FaBel" [25]), which assesses the burden of parenting a chronically ill or disabled child using 33 items, rated on a 4-point Likert-scale. It provides a total impact score encompassing four dimensions of stress (daily psychosocial distress, 15 items; financial strain, 4 items; personal strain & fears for the future, 5 items; difficulties with coping, 3 items). The total impact score comprises a scale from 27 to 108 with higher scores indicating more caregiver burden.

In an online-survey the metabolic physicians provided the *specific IT-IEM diagnosis*, which was classified as "non-acute" or "acute" IT-IEM by the research team.

*Patients' sex* (0 = male, 1 = female) and *age at assessment* were reported by the participating children/adolescents and their parents respectively.

### 2.3. Statistical procedure

The statistical software package SPSS, version 27 for Windows, was used to carry out the statistical analyses [26]. A significance level of  $p < .05$  was set for all tests. The handling of missing data was omitted since all survey items were mandatory per default. A three-step hierarchical regression analysis was conducted to determine predictors of self- and parent-reported HrQoL. Step one included patient sex, and patient age at assessment. In step two, patients' dichotomously coded diagnosis was entered (0 = non-acute IT-IEM, 1 = acute IT-IEM). In step three, parent rated disease severity and parent rated caregiver burden were added to the model.

Mediation analyses were conducted with the PROCESS macro for SPSS version 4.0 [27]. The potential mediating role of caregiver burden ( $M$ ) between parental perceived disease severity ( $X$ ) and patients' HrQoL ( $Y$ ) was investigated (see Fig. 1). Concretely, caregiver burden was expected to conceptualize the intervening mechanism through which parental severity perception influences patients' HrQoL. Bootstrap confidence intervals (number of bootstraps = 5000) were used to test the indirect effect ( $c'$  = severity rating on HrQoL through caregiver burden) for significance. Estimates for the model parameters were only interpreted if the indirect effect was significant (if confidence intervals

did not contain zero [27]). Two separate models for self-reported and parent-reported HrQoL as the dependent variable Y were analysed. Under the assumption of violation of homoscedasticity for parent-reported HrQoL as dependent variable, a heteroscedasticity -consistent standard error estimator (HC4) was used to test the model parameters for significance [28].

### 3. Results

#### 3.1. Sample characteristics

Tables 1 and 2 show the characteristics of the study samples and the analyses of parent-, and patient-reported data. HrQoL reports were available from 50 parents and 35 paediatric IT-IEM patients. Parent and patient HrQoL-reports showed a strong positive correlation (Pearson product-moment correlation coefficient  $r = 0.79$ ;  $p < .01$ ) [29]. All 16 acute IT-IEM patients rated by parents were hospitalised due to metabolic decompensations ( $n = 7$  1–5 times;  $n = 2$  6–10 times;  $n = 2$  11–15 times;  $n = 2$  16–20;  $n = 3$  > 20 times). Accordingly all 12 acute IT-IEM patients in the subsample who self-reported their HrQoL, were hospitalised at least once ( $n = 7$  1–5 times;  $n = 2$  6–10 times;  $n = 2$  11–15 times;  $n = 1$  16–20 times).

Of the participating parents 16% reported a university degree ( $n = 7$  mothers,  $n = 1$  father), 34% a degree on high-school level ( $n = 16$  mothers,  $n = 1$  father), 46% a completed apprenticeship ( $n = 22$  mothers,  $n = 1$  father), and 4% a completion of obligatory education ( $n = 2$  mothers). Eighty percent of parents reported being in payed employment ( $n = 37$  mothers,  $n = 3$  fathers; Median stint = 55%, SD = 15.2%, range = 20%–100%).

#### 3.2. Regression analyses

As shown in Table 3, the final model with parent-reported HrQoL of IT-IEM patients as dependent variable was significant and accounted for approximately 67% of the variance. The stepwise approach revealed that the first model including patients' age at assessment & patients' sex was not significant. Model 2, with the addition of type of diagnosis turned out significant. The third model under inclusion of parental perceived disease severity & care giver burden was significant and explained most of the variance. Patients' HrQoL was rated lower by parents who perceived their child's disease to be more severe and who experienced a higher caregiver burden. "Type of diagnosis", initially a significant predictor in model 2, lost its significance after the addition of "parental parameters". Patients' age at assessment and patients' sex were no significant predictors of proxy-rated HrQoL.

As shown in Table 4, the equivalent final model with patient-reported HrQoL as the outcome was significant. Model 3 accounted for approximately 59% of variance (significantly more than model 1 and

**Table 1**  
Characteristics of the sample with parent-reported HrQoL.

	Total sample	Acute IT-IEM	Non-acute IT-IEM
<b>Parent sample</b>			
Total (n)	50	16	34
Mothers (n/%)	47 (94.0)	15 (93.7)	32 (94.1)
Fathers (n/%)	3 (6.0)	1 (6.3)	2 (5.9)
<b>Family nationality (n/%)</b>			
Switzerland	19 (38.0)	2 (12.5)	17 (50.0)
Germany	11 (22.0)	6 (36.0)	5 (15.0)
Austria	10 (20.0)	5 (32.0)	5 (15.0)
Italy	3 (6.0)	1 (6.5)	2 (5.5)
Romania	2 (4.0)	1 (6.5)	1 (3.0)
Turkey	2 (4.0)	–	2 (5.5)
Kosovo	1 (2.0)	–	1 (3.0)
Mexico	1 (2.0)	–	1 (3.0)
Serbia	1 (2.0)	1 (6.5)	–
HrQoL total score (pr; Mean/SD)*	77.3 (12.2)	71.2 (15.2)	80.2 (9.4)
Parental severity rating** (Mean/SD)	9.5 (17.4)	15.6 (25.6)	6.6 (11.2)
Caregiver burden*** (Mean/SD)	43.6 (13.3)	50.2 (18.5)	40.5 (8.8)
<b>Parent-rated patients (n/%)</b>			
Total (n)	50	16	34
Female (n/%)	26 (52.0)	11 (68.7)	15 (44.1)
Male (n/%)	24 (48.0)	5 (31.3)	19 (55.9)
Patients' age at assessment in years (Mean/Range, SD)	11.4 (5–19, 3.7)	11.4 (6–18, 3.9)	11.4 (5–19, 3.6)

Abbreviations: IT-IEM, intoxication-type inborn errors of metabolism; SD, standard deviation, HrQoL, health-related quality of life; pr, parent-reported.

Notes: Summary of patients in the acute IT-IEM subgroup:  $n = 9$  OA-patients (56.3%;  $n = 3$  PA,  $n = 3$  GA1,  $n = 2$  IVA,  $n = 1$  MMA),  $n = 6$  UCD-patients (37.5%;  $n = 4$  OTC deficiency,  $n = 2$  ASS1 deficiency),  $n = 1$  MSUD-patient (6.2%).

\* Lowest HrQoL score = 0, highest HrQoL score = 100.

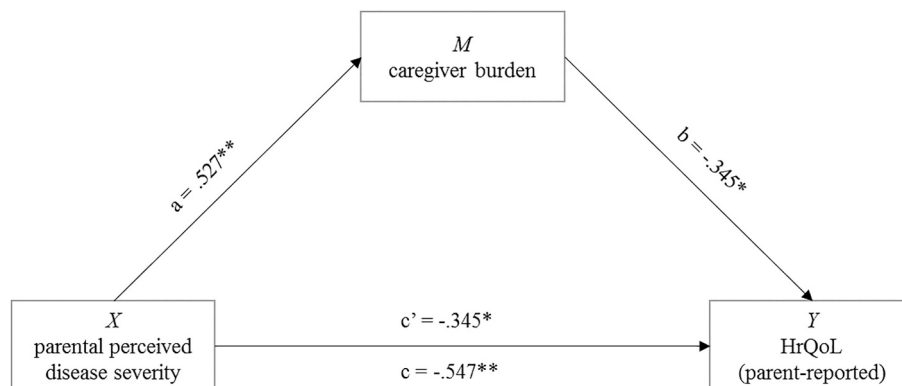
\*\* Lowest severity score = 0, highest severity score = 100.

\*\*\* Lowest score for caregiver burden = 27, highest score for caregiver burden = 108.

2). Female sex predicted significantly lower self-reported HrQoL. Beyond this, both parental perceived disease severity and parent-reported caregiver burden were significant negative predictors of patient-reported HrQoL.

#### 3.3. Mediation analyses

For parent-reported HrQoL of IT-IEM patients as the outcome Y the bootstrapped mediation analysis supported the hypothesised model (see Fig. 1). Increasing parent-rated severity predicted higher caregiver burden, which in turn predicted lower parent-reported HrQoL. The confidence interval of the indirect effect suggests a significant mediation. The model accounted for approximately 68.5% of variance in



**Fig. 1.** Mediation model of parent-reported caregiver burden mediating the association between parental perceived disease severity and parent-reported HrQoL of IT-IEM patients ( $n = 50$  parents).

Notes: Estimate of the indirect effect = (0.26); 95% bootstrap confidence interval = (-0.494, -0.040). The displayed path coefficients constitute the unstandardized B weights. Path c' refers to the effect of perceived disease severity on parent-reported HrQoL under inclusion of caregiver burden as the mediator. Path c refers to the effect of perceived disease severity on parent-reported HrQoL while caregiver burden as mediator is excluded. Path a refers to the effect of perceived disease severity on caregiver burden. Path b refers to the effect of caregiver burden on parent-reported HrQoL under inclusion of perceived disease severity as the intervening variable.

\*\* $p < .001$ , \* $p < .05$ .

**Table 2**  
Characteristics of the sample with patient-reported HrQoL.

	Total sample	Acute IT-IEM	Non-acute IT-IEM
Patient sample (n/%)			
Total (n)	35	12	23
Female (n/%)	16 (45.7)	8 (70.6)	8 (34.8)
Male (n/%)	19 (54.3)	4 (33.3)	15 (65.2)
Family nationality (n/%)			
Switzerland	13 (37.0)	2 (17.0)	11 (49.0)
Germany	7 (20.0)	3 (25.0)	4 (18.0)
Austria	8 (23.0)	5 (42.0)	3 (13.0)
Italy	2 (5.5)	1 (8.0)	1 (4.0)
Romania	2 (5.5)	1 (8.0)	1 (4.0)
Turkey	1 (3.0)	–	1 (4.0)
Kosovo	1 (3.0)	–	1 (4.0)
Mexico	1 (3.0)	–	1 (4.0)
Serbia	–	–	–
Age at assessment in years (Mean/Range, SD)	12.0 (7–19, 3.5)	12.0 (7–18, 3.9)	12.0 (7–19, 3.4)
HrQoL total score (sr; Mean/SD) <sup>a</sup>	80.01 (15.7)	79.0 (21.3)	80.5 (12.5)
Parental severity rating <sup>**</sup> (Mean/SD)	8.57 (16.3) <sup>a</sup>	10.42 (21.9) <sup>b</sup>	7.6 (12.9) <sup>c</sup>
Caregiver burden <sup>***</sup> (Mean/SD)	42.4 (12.6) <sup>a</sup>	23.4 (7.4) <sup>b</sup>	40.25 (9.0) <sup>c</sup>

Abbreviations: IT-IEM, intoxication-type inborn errors of metabolism; SD, standard deviation, HrQoL, health-related quality of life; sr, self-reported.

Notes: Summary of patients in the acute IT-IEM subgroup: n = 6 OA-patients (50.0%; n = 2 PA, n = 2 GA1, n = 1 IVA, n = 1 MMA), n = 5 UCD-patients (41.7%; n = 4 OTC deficiency, n = 1 ASS1 deficiency), n = 1 MSUD-patient (8.3%).

<sup>a</sup> Corresponding parent-reports n<sub>total</sub> = 35 (34 mothers, 97.1%).

<sup>b</sup> Corresponding parent-reports n<sub>acute</sub> = 12 (11 mothers, 91.7%).

<sup>c</sup> Corresponding parent-reports n<sub>non-acute</sub> = 23 (23 mothers, 100%).

\* Lowest HrQoL score = 0, highest HrQoL score = 100.

\*\* Lowest severity score = 0, highest severity score = 100.

\*\*\* Lowest score for caregiver burden = 27, highest score for caregiver burden = 108.

parent-reported patients' HrQoL. The equivalent mediation model with patient-reported HrQoL as the outcome Y was nonsignificant.

#### 4. Discussion

Despite major progress in the medical treatment of IT-IEM there is still limited knowledge about paediatric patients' HrQoL and even less about its determinants and underlying processes, which could be valuable targets for interventions. In this multicenter survey study the impact of sociodemographic factors, type of diagnosis, parent-perceived disease severity and caregiver burden on patients' HrQoL was investigated. The results emphasize the importance of parental factors for HrQoL of patients with IT-IEM.

**Table 3**  
Hierarchical regression with parent-reported HrQoL as dependent variable (n = 50 parents).

	Model 1				Model 2				Model 3			
	B	SE B	β	p	B	SE B	β	p	B	SE B	β	P
<b>1: Sociodemographic factors</b>												
Patients' sex	−3.07	3.46	−0.13	0.38	−1.2	3.38	−0.05	0.70	0.78	2.10	0.03	0.72
Patients' age at assessment	−0.49	0.48	−0.15	0.37	−0.49	0.45	−0.15	0.35	−0.21	0.28	−0.10	0.51
<b>2: Medical severity</b>												
Diagnosis (dichotomous)					−8.77	3.62	−0.34	<b>0.036</b>	−2.94	2.32	−0.06	0.267
<b>3: Parental parameters</b>												
Perceived disease-severity									−0.36	0.08	−0.51	<b>0.004</b>
Caregiver burden									−0.32	0.12	−0.35	<b>0.038</b>
<b>Change in R<sup>2</sup></b>												
					R <sup>2</sup> <sub>change</sub> = 0.109*				R <sup>2</sup> <sub>change</sub> = 0.554**			
					F(3,49) = 2.622,				F(5,49) = 20.513,			
					p = .062;				p < .001;			
<b>Model fit</b>					adjusted R <sup>2</sup> = −0.004				adjusted R <sup>2</sup> = 0.666			
					F(2,49) = 0.910,							
					p = .410;							
					adjusted R <sup>2</sup> = −0.004							

\*\*p < .001, \*p < .05.

High caregiver burden constituted a meaningful risk factor for lower patients' HrQoL. This effect has also been observed in paediatric diabetes or epilepsy [30,31]. It has been hypothesised that high caregiver burden results in ineffective parenting styles (e.g. criticism and rejection) and a general negative emotional family environment [8]. This association is particularly alarming, because parents of chronically ill children consistently exhibit increased levels of distress and caregiver burden [12,32–34]. Specific care burdens in IT-IEM encompass the subsidiary fear of impaired adherence to or effect of treatment with severe health consequences for the child, as well as social restrictions e.g. due to dietary treatment [1,3,10]. Dietary treatment appears to be a serious source of strain for parents. It requires effort, is burdensome and time-consuming, and often associated with conflicts and disputes within the family [35]. These potential conflict situations occur several times daily in affected families and may not only foster ineffective parenting behaviours but also an overall tense atmosphere.

Parents' subjective perception of their child's disease severity is another significant negative predictor of patients' HrQoL. It is important for metabolic teams to realize that the subjective impression of the parents is much more important and predictive than the "objective" clinical type of diagnosis (acute vs. non-acute). The limited predictive power of clinical diagnostic categories for psychosocial outcomes has been reported in several chronic conditions [8,36]. We suggest to routinely include patient- and parent-reported parameters such as severity assessments not only into psychosocial research but also into routine care.

Female patients reported lower HrQoL compared to males. This sex difference was also found in our earlier work on a large international sample of paediatric IT-IEM patients [5]. Explanations are manifold and encompass differences regarding social demands and coping styles [37]. Female patients may be more adjusted and well-behaved in medical consultations, which might increase the risk of missing potential HrQoL impairments while males tend to displaying their constraints more externally, which might make the provision of targeted support easier [38]. Further studies are required to better understand the dynamics of HrQoL for female IT-IEM patients and to draw conclusions regarding sex-specific intervention.

Caregiver burden mediates the association between parental perception of disease severity and patients' parent proxy-reported HrQoL. High attributed severity is associated with higher caregiver burden, which in turn predicts significantly lower proxy-reported HrQoL. The mediation model for the small numbers of patient self-reports on HrQoL may reflect a weaker statistical power. The alternative explanation that proxy and self-reported patients' HrQoL may be generally different is contradicted by the high correlation between the two sources.

Beyond its mediating role, caregiver burden constitutes in its own



**Table 4**  
Hierarchical regression with patient-reported HrQoL as dependent variable  
( $n = 35$  patients).

	Model 1				Model 2				Model 3			
	B	SE B	$\beta$	$p$	B	SE B	$\beta$	$p$	B	SE B	$\beta$	$P$
<b>1: Sociodemographic factors</b>												
Patients' sex	-10.80	5.15	-0.35	<b>0.044</b>	-11.42	5.48	-0.37	<b>0.046</b>	-9.17	3.62	-0.30	<b>0.017</b>
Patients' age at assessment	-0.26	0.75	-0.06	0.73	-0.26	0.76	-0.06	0.73	-0.49	0.50	-0.01	0.92
<b>2: Medical severity</b>												
Diagnosis (dichotomous)					2.12	5.75	0.07	0.72	4.94	3.85	0.15	0.21
<b>3: Parental parameters</b>												
Perceived disease-severity									-0.47	0.14	-0.48	<b>0.002</b>
Caregiver burden									-0.41	0.18	-0.33	<b>0.031</b>
<b>Change in <math>R^2</math></b>												
					$R^2_{\text{change}} = 0.004$				$R^2_{\text{change}} = 0.522^{**}$			
<b>Model fit</b>	$F(2,34) = 2.269,$ $p = .120;$ Adjusted $R^2 = 0.069$				$F(3,34) = 1.517,$ $p = .230;$ Adjusted $R^2 = 0.044$				$F(5,34) = 10.752,$ $p < .001;$ Adjusted $R^2 = 0.589$			

\*\* $p < .001$ , \* $p < .05$ .

right a significant risk factor for (proxy- and self-reported) HrQoL and needs thus to be considered and approached in daily health care.

Encouragingly, data from a meta-analysis of the effects of targeted interventions yielded significantly positive effects of psychological interventions for parents of chronically ill children. Cognitive-behavioural therapy (CBT) and problem-solving therapy (PST) have long-term positive effects on parents' emotional distress and maladaptive parenting behaviour such as overprotective responses (only PST) [39]. These approaches could be helpful for parents of IT-IEM patients with high caregiver burden, and their children. When targeting caregiver burden in IT-IEM, health care providers must be aware of meaningful parental perceptions and narratives about their child's disease.

The strengths of this study are the multicentric recruitment to reach a meaningful sample size and the inclusion of a disease-specific HrQoL measure. The *MetabQoL* addresses specific issues and thus improves the acceptance of the survey among participating families.

The most important limitations are the conduct of this study during the COVID-pandemic which seems associated with an increased risk for mental-health problems in children and adolescents [40] as well as an elevated caregiver burden in parents [41]. It is likely, that pandemic-related sequels for families have affected the investigated variables and presented study results. Furthermore, the sample sizes only allowed for the inclusion of a limited number of sociodemographic and medical predictors into the statistical models. The restricted number of self-reports led to a significant loss of statistical power. In the parent sample, the father perspective was clearly underrepresented which is a common issue in this research field [42]. The cross-sectional design of the study does not allow for causal conclusions; all discussed relations are of a correlative nature. Longitudinal studies could be useful to explore developmental and long-term effects of caregiver burden on patients' HrQoL. Follow-up studies would also enable the investigation of pandemic-related confounding effects. The restriction to German-speaking families limits the representativity of the results. A broader approach across different languages and cultures may be facilitated by a recent review of standardised patient- and parent-reported outcome measures allowing for cross-cultural comparisons in IT-IEM [43].

## 5. Conclusion

This international, multicenter survey study provides first quantitative evidence for the crucial role of caregiver burden and disease severity assessment of parents for HrQoL of paediatric patients with IT-IEM. Interventions targeting this could be promising options to support parents experiencing high caregiver burden and to reduce negative consequences for their children. Parents' severity assessment of their children's disease appeared to be an important predictor of patients' HrQoL. This finding underscores the importance of integrating parental

perceptions towards their child's disease in both interventional programs and daily health care. Furthermore, this study highlights the need for awareness towards signs of impaired HrQoL in females with IT-IEM.

The encouraging evidence gained from other chronic conditions on the effectiveness of interventions such as cognitive-behavioural therapy for parents needs to be investigated in families of children with IT-IEM in controlled, prospective intervention studies.

## Details of ethical approval

The usage of patient data in this study was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the ethical committee in Zurich, Switzerland (KEK-ZH Nr. 2020.02227), and the local ethical committees Bern, Basel, Freiburg, and Innsbruck. All participants gave their informed consent.

## Details of the contributions of individual authors

F.B. was involved in designing the study, collected and analysed the data, and drafted the manuscript. C.H. was involved in collecting and analysing the data. S.F., M.G., S.C.G., D.K., D.L., S-S-B., G.S., contributed patient data. M.R.B., P.F., J.H., M.R., were involved in coordination of the study and contributed patient data. M.A.L., was involved in designing the study, gave advice on data collection, supervised data analysis, and critically reviewed the manuscript. M.H. developed the original concept of the study, coordinated the study, and revised the manuscript. All authors read and approved the final version of the manuscript.

## Declaration of Competing Interest

The authors of this manuscript declare no competing interests but disclose the following:

F. Bösch, M.A. Landolt, S. Fernandez, P. Forny, M. Gautschi, S.C. Grünert, C. Horvath, D. Karall, D. Lampis, M. Rohrbach, and Gabor Szinnai report that they have nothing to disclose. M. R. Baumgartner received a research fund from Nutricia Metabolics and is a member of the clinical advisory boards of Hemoshear and Moderna. J. Häberle has received a research grant from Nutricia Metabolics and is collaborating in research with Recordati Rare Diseases. S. Scholl-Bürgi has received travel support from Nutricia Metabolics. M. Huemer has received research grants from Nutricia Metabolics and consultancy honoraria from Aeglea, Nutricia Metabolics, Sanofi, Shire, SOBI, and Orphan Europe.

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