



Understanding the impact of long-chain fatty acid oxidation disorders for patients and caregivers

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ABSTRACT

Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of rare, autosomal recessive genetic disorders that impair conversion of long-chain fatty acids into energy. Here we describe the impact of LC-FAOD in terms of effects on work and school, absenteeism and presenteeism at work, importance of symptoms, physical activity, participation in social activities, and quality of life (QoL). A convenience sample of adults (≥ 18 years) and caregivers of patients with LC-FAOD was invited to take the online survey (Conformit). To be included, patients must have been receiving medical care from a healthcare provider for their LC-FAOD, and caregivers must not have been compensated for their care. Degree of physical activity, represented by metabolic equivalents (METs), was calculated using the NHANES Physical Activity Questionnaire. Absenteeism and presenteeism at work were calculated using the WHO Health Productivity Questionnaire. QoL was assessed using the 12-Item Short Form of the Medical Outcomes Survey. Significance was assessed using two tailed independent sample *t*-tests and *z*-tests at $\alpha = 0.1$. Fourteen adults and 30 caregivers of LC-FAOD patients (answering for 37 patients) answered the survey (51 unique respondents). 59.2% of LC-FAOD patients experienced effects on their schooling due to LC-FAOD. 84.2% of working patients experienced effects on their work due to LC-FAOD. 70% of caregivers experienced effects on their work due to their child's LC-FAOD. Unique respondents report that muscle weakness (69%), physical fatigue (49%), and rhabdomyolysis (39%) are the most impactful symptoms of LC-FAOD. Adults ($n = 14$) scored significantly below the normalized average (50) on both physical (34.51, $p < 0.001$) and mental (45.27, $p = 0.04$) component scores of the SF-12 health-related quality of life measure. LC-FAOD impart a high disease impact on patients and their caregivers. In particular, symptoms relating to energy production were rated as highly impactful and limiting. Activities that may be considered normal for many people can prove to be very difficult or impossible for respondents with LC-FAOD, with respondents reporting lower physical and mental health-related quality of life measures than the average American.

1. Introduction

Long-chain Fatty Acid Oxidation Disorders (LC-FAOD) are a group of rare, life-threatening autosomal recessive disorders [1,2] caused by defects in mitochondrial β -oxidation enzymes or the carnitine shuttle, which are components of the metabolic pathway by which long-chain fatty acids are converted to energy [3,4]. There are 6 enzyme deficiencies associated with LC-FAOD: very long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), carnitine palmitoyl transferase 1 (CPTI), carnitine palmitoyl transferase 2 (CPTII), carnitine/acylcarnitine translocase (CACT), and

trifunctional protein (TFP) [5]. Clinical manifestations of LC-FAOD include manifestations of energy deficiency such as rhabdomyolysis and hypoglycemia (61% and 79% respectively in a study of 187 French children living with LC-FAOD) [6]. Toxic metabolite build-up as a result of LC-FAOD can lead to complications in a wide range of organs and may affect the heart (cardiomyopathy), eyes (retinopathy), and nervous system (neuropathy) [1,6].

LC-FAOD may be treated using a combination of dietary management and supplementation with medium-chain triglycerides (MCTs) [3]. Previously, the core treatment regimen for LC-FAOD consisted of low-fat diet with supplementation of a homogeneous mixture of even-chain

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MCTs [7]. Additionally, lifestyle modifications such as avoidance of fasting, frequent meals, and exercise limitation/avoidance have been used to avoid negative side effects that may be associated with LC-FAOD [7]. Triheptanoin, a 7-carbon MCT with anaplerotic properties [3] was approved in the United States in 2020 as a source of calories and fatty acids for the treatment of pediatric and adult individuals with molecularly confirmed LC-FAOD [8].

The symptoms experienced by individuals with LC-FAOD are understood to have a substantial limiting impact on physical, mental, and social aspects of their lives, but to date, this impact has not been quantified in a rigorous study. These impacts are variable and can be associated with lower quality of life for individuals with LC-FAOD and those that care for them [9,10]. Individuals may require round-the-clock care, which can place enormous stress on their caregivers. The high impact of care in metabolic diseases has been shown to lead to increased rates of anxiety in caregivers and may affect multiple aspects of their lives including work and interpersonal relationships [11,12].

The key objective of this study was to quantify the impact of LC-FAOD on individuals with LC-FAOD and caregivers of those individuals during everyday life, by collecting and analyzing data in key areas, including effects on work and school, effects on absenteeism, presenteeism, amount of work missed, effects on physical activity, and QoL. To determine these impacts, we have conducted an institutional review board (IRB)-approved survey of individuals with LC-FAOD and caregivers of individuals with LC-FAOD.

2. Methods

We report here the results of an online quantitative survey administered to adult individuals with LC-FAOD and caregivers of individuals with LC-FAOD. Data were collected from 10 February 2020 to 24 March 2020. To participate in the survey, adults living with LC-FAOD must have been 18+ years old and have a formal diagnosis of LC-FAOD. Caregivers must have cared for at least one individual with LC-FAOD, must not have been compensated for care of individuals with LC-FAOD in a healthcare provider capacity, and must have not cared for an adult who had already taken the survey. Participants were recruited via a combination of an internal panel of known individuals with LC-FAOD and external engagement enterprises SNOW Companies [13] and Rare Patient Voice [14]. The study protocol and materials received IRB approval from Pearl IRB [15]. This study was carried out in accordance with the Declaration of Helsinki. All respondents provided informed consent prior to initiating the survey.

The survey content was developed using a targeted review to identify knowledge gaps in existing LC-FAOD literature in conjunction with feedback provided by patient and caregiver consultants and was then refined by conducting pre-tests with LC-FAOD treating physicians, individuals with LC-FAOD, and caregivers of individuals with LC-FAOD.

The survey was programmed by OWL Programming [16] and administered via Confront, an online survey hosting platform. The survey took roughly 30 min and patients were compensated at a rate of \$110/h for their time, which translated to \$55 for a survey covering one patient with LC-FAOD, \$75 for a survey covering two patients, and \$95 for a survey covering three patients. Payments were made via a check or online transfer. Data were anonymized using unique patient identifiers in place of names. The survey was divided into 6 categories: *Diagnosis, Disease Management and Treatment; Impact of LC-FAOD; Assessment of Absenteeism and Presenteeism at Work and School; Physical Activity and Fitness; and Quality of Life*. See Supplemental Table 1 for a redacted survey showing the questions that are reported in this study. Considerations for data analysis are described below.

2.1. Impact of LC-FAOD

In this section, adults living with LC-FAOD reported only on themselves, while caregivers reported both on impacts that LC-FAOD has had

on their child's education and employment, as well as impacts that LC-FAOD has had on their own education and employment. Individuals with LC-FAOD or their caregivers were asked to rank the following symptoms from 1 to 12 based on the impact each has: physical fatigue, mental fatigue, rhabdomyolysis, heart conditions, hypoglycemia, muscle weakness and functional impairment, exercise intolerance, eye conditions, peripheral neuropathy, motor delays, speech delays, and cognitive delays. Symptoms LC-FAOD symptoms were considered highly impactful if they were ranked in the top 3 symptoms.

2.2. Assessment of absenteeism and presenteeism at work and school

In this section, employed adults living with LC-FAOD reported on themselves, while employed caregivers also reported on themselves.

The World Health Organization (WHO) Health Productivity Questionnaire (HPQ) was used to calculate absenteeism and presenteeism, as described in Kessler 2003 [17]. Absolute and relative absenteeism were defined as the number of working hours missed in the past 4 weeks and the ratio of working hours missed to the total hours expected to work, respectively. Absolute and relative presenteeism were defined as the ratio of subjective performance at work compared to a top worker and the ratio of subjective performance at work compared to an average worker, respectively. This study used control group data for presenteeism found in the National Comorbidity Survey Replication study (NCS-R) [18] and control group data for the days of work missed in the past 12 months taken from the United States Bureau of Labor Statistics [19]. Comparator data for days of work missed in the past 6 months was defined as half of the control value for days of work missed in 12 months.

2.3. Physical activity and fitness

The National Health and Nutrition Examination Survey (NHANES) Physical Activity Questionnaire (PAQ) [20] was used to calculate metabolic equivalents (METs) and determine whether individuals with LC-FAOD were meeting weekly recommended levels of physical activity for adults. This study also utilized control values for weekly physical activity, found in the WHO Prevalence of Insufficient Physical Activity Among Adults report [21]. The calculation used to determine METs was [20]:

$$(\text{Minutes of vigorous work activity per week} * 8) + (\text{Minutes of vigorous recreational activity per week} * 8) + (\text{Minutes of moderate work activity per week} * 4) + (\text{Minutes of moderate recreational activity per week} * 4) + (\text{Minutes of cycling and walking per week} * 4).$$

2.4. Quality of life

The 12-Item Short Form of the Medical Outcomes Survey (SF-12) [22] was used to assess QoL. The SF-12 is a widely used general health questionnaire that measures general quality of life across 8 different domains physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Optum Health Services [23] was employed to analyze these data using a proprietary formula to calculate Physical and Mental Composite Scores (PCS/MCS), which represent physical and mental QoL on a 0–100 scale with an average of 50 and a standard deviation of 10. This transformation enables comparison of the study population with a broader population, with an overall score above 50 indicating better than average functioning and any score below 50 indicating below average functioning [24]. A score of 50 or less on the PCS-12 has been recommended as a cut-off to determine a physical condition; while a score of 42 or less on the MCS-12 may be indicative of clinical depression [24].

2.5. Data cleaning

Three caregiver responses were removed from the data set as the

adult patients that they care for also completed the survey. Three sets of caregivers answered the survey for the same person; their answer records were reconciled with only one set of data included in the analysis for each patient. One caregiver's responses were cleaned from education analysis due to marking "currently in preschool" for their own education status. One response was cleaned from the "Impact on Work" section as an outlier, having reported >300% of expected hours worked in the past 28 days.

2.6. Statistical analysis

Descriptive statistics were reported for the sample population. Patients with TFP deficiency were included in analysis of the total population but were excluded from comparison between LC-FAOD types due to small sample size. Significant differences between proportions and means described for enzyme deficiencies and age groups were determined using independent samples Student's *t*-tests using $\alpha = 0.10$. For QoL measures, significant differences were determined using *z*-tests at $\alpha = 0.10$ due to the presence of a normalized population comparator.

2.7. Data sharing statement

Due to the rarity of LC-FAOD and the small number of patients and caregivers in this study, individual patient and caregiver data will not be shared in order to safeguard privacy, consistent with the data sharing policy listed on Ultragenyx.com.

3. Results

We report here the results of an online quantitative survey administered to 44 respondents. After data cleaning, records from 44 respondents have been analyzed, including 14 adult individuals with LC-FAOD and 30 caregivers reporting on 37 individuals with LC-FAOD. Unless specified otherwise, results are reported for individuals with LC-FAOD whether reported by a caregiver or directly from an individual with LC-FAOD. The sample represented an age range of 8 months – 67 years and had a mean age of 16.25 years. Most individuals with LC-FAOD were < 18 years old (60.8%). Both sexes were well-represented, with slightly more males (55%). Slightly fewer of the individuals were diagnosed via newborn screening (NBS) (45%). An LCHAD diagnosis made up 39.2% of the individuals, VLCAD 31.4%, CPT II 25.5%, and TFP 3.9%; none of the individuals had a diagnosis of CPT I or CACT. Further information is available in [Tables 1 and 2](#) and Supplemental Table 4.

3.1. Individuals with LC-FAOD vs. caregiver comparisons

Nearly all individuals with LC-FAOD had attended some form of school ($n = 49$). Many (59.2%) experienced at least one impact of LC-FAOD on their schooling, with the most frequent being a reduction in study load (24.5%). However, several individuals with LC-FAOD also experienced "other impacts" (28.6%), which included creating Individualized Education Plans (IEPs) to accommodate their LC-FAOD or staying home/attending fewer days per week.

Of caregivers eligible to work ($n = 30$), the majority (70%) reported at least one impact of their child's LC-FAOD on their work, but these were distributed across a broad range of impacts including changing jobs (36.7%), stopping working (36.7%), reducing their working hours (33.3%), and turning down job opportunities (23.3%). The reasons for these impacts were also varied, with the top reason for impact being their child's hospitalizations (56.7%).

The 9 working caregivers of individuals with LC-FAOD reported an average of 9.7 h (representing 9% of total hours) lost per month, and the 19 working adults living with LC-FAOD reported an average of 7.9 h lost per month (representing 6% of total hours). Working adults living with LC-FAOD reported substantially lower absolute presenteeism than a control group of American workers (74% vs 84%). When looking at

Table 1

Characteristics – Age, Type, NBS Status, Treatment Use.

Sex of individuals with LC-FAOD (% , n)	All ages (N = 51)	Children (N = 31)	Adults (N = 20)
Male	55%, 28	65%, 20	40%, 8
Female	45%, 23	35%, 11	60%, 12
Age of individuals with LC-FAOD			
Mean	16.25 years	8.0 years	26.7 years
Median	14.0 years	6.0 years	24.5 years
Range	8 months – 67 years	8 months – 17 years	18 years – 67 years
Enzyme deficiencies (% , n)			
LCHAD	39.2%, 20	42%, 13	35%, 7
VLCAD	31.4%, 16	35%, 11	15%, 5
CPT II	25.5%, 13	19%, 6	35%, 7
TFP	3.9%, 2	3%, 1	5%, 1
Individuals with LC-FAOD diagnosed via NBS* (% , n)			
Diagnosed via NBS	45%, 23	74%, 23	0%, 0
Not diagnosed via NBS	55%, 28	26%, 8	100%, 20
Experience with triheptanoin (C7/DOJOLVI) or MCT products (% , n)			
Only triheptanoin/C7/DOJOLVI	11%, 5	6.5%, 2	15%, 3
Only MCT products	66%, 34	74%, 23	55%, 11
Both triheptanoin/C7/DOJOLVI and MCT products	24%, 12	19%, 6	30%, 6
Neither triheptanoin/C7/DOJOLVI nor MCT products	0%, 0	0%, 0	0%, 0
Current use of triheptanoin (C7/DOJOLVI) or MCT products (% , n)			
Only triheptanoin/C7/DOJOLVI	27.5%, 14	26%, 8	30%, 6
Only MCT products	62.7%, 32	71%, 22	50%, 10
Both triheptanoin/C7/DOJOLVI and MCT products	0%, 0	0%, 0	0%, 0
Neither triheptanoin/C7/DOJOLVI nor MCT products	9.8%, 5	3%, 1	20%, 4

Abbreviations used: LC-FAOD, long-chain fatty-acid oxidation disorders; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; VLCAD, very long-chain acyl-CoA dehydrogenase; CPTII, carnitine palmitoyl transferase 2; TFP, tri-functional protein; NBS, newborn screening; MCT, medium-chain triglyceride.

* Adults living with LC-FAOD were assumed to not be diagnosed via NBS.

relative presenteeism, or comparison of work performance to an average worker in the respondent's role, all groups reported above average performance, but both working patients and caregivers reported less exceptional performance than the control group (patients: 105%, caregivers: 106%, control group: 117%). Both working adults living with LC-FAOD and working caregivers of individuals with LC-FAOD reported missing substantially more days of work in the past 6 months (individuals with LC-FAOD: 3.3 days, caregivers: 6.2 days, control: 1.4 days) and 12 months (individuals with LC-FAOD: 5.7 days, caregivers: 10.5 days, control: 2.8 days) than a control group of American workers. Full results are available in [Table 3](#).

3.2. Age comparisons

Among individuals with LC-FAOD, 16 were < 7 years old, 15 were 7–17 years old, and 20 were ≥ 18 years old. Patients were given the following symptoms to rank based on the impact of the symptom on the patient and caregiver's life: physical fatigue, mental fatigue, rhabdomyolysis, heart conditions, hypoglycemia, muscle weakness and functional impairment, exercise intolerance, eye conditions, peripheral neuropathy, motor delays, speech delays, and cognitive delays. Overall, muscle weakness was consistently chosen among the most impactful

Table 2
Characteristics – Education and Employment Status.

Current Education Status (% <i>n</i>)	All individuals with LC-FAOD < 19 years old (<i>N</i> = 32)	All individuals with LC-FAOD ≥ 19 years old (<i>N</i> = 19)	All caregivers (<i>N</i> = 29) †
Too young to enroll in education	6%, 2	0%, 0	–
Preschool / kindergarten	38%, 12	0%, 0	–
Lower school (1st – 8th grade)	31%, 10	5%, 1*	–
High school (9th – 12th grade)	22%, 7	0%, 0	–
Post-secondary education (e.g. university or trade school)	0%, 0	16%, 3	–
Graduate or professional school	0%, 0	16%, 3	3%, 1
Not currently enrolled in education	3%, 1	63%, 12	97%, 28
Highest Previous Education Achieved (%<i>n</i>)	All individuals with LC-FAOD ≥ 18 years old not currently enrolled in education (<i>N</i> = 12)	All caregivers not currently enrolled in education (<i>N</i> = 28) †	
Preschool / kindergarten	0%, 0	0%, 0	
Lower school (1st – 8th grade)	0%, 0	0%, 0	
High school (9th – 12th grade)	25%, 3	7%, 2	
Post-secondary education (e.g. university or trade school)	42%, 5	36%, 10	
Graduate or professional school	33%, 4	57%, 16	
Current Employment Status (%<i>n</i>)	Individuals with LC-FAOD ≥ 18 years old (<i>N</i> = 20)	All caregivers (<i>N</i> = 30)	
Full time (≥35 h/week, regular hours)	25%, 5	50%, 15	
Part time (<35 h/week, regular hours)	30%, 6	7%, 2	
Part time (variable hours)	15%, 3	13%, 4	
Unemployed or not seeking employment	10%, 2	23%, 7	
Too young to work or still pursuing education	5%, 1	–	
Retired	0%, 0	3%, 1	
Cannot work due to LC-FAOD / child's LC-FAOD	15%, 3	3%, 1	

Abbreviations used: LC-FAOD, long-chain fatty-acid oxidation disorders

* Due to other responses from their caregiver, the research team concluded that this patient likely has special needs, rather than their education level having been reported in error.

† Caregiver responses describe the caregivers themselves, rather than the individuals with LC-FAOD. One caregiver's responses were cleaned from the education status section

Table 3
Comparison of Individuals with LC-FAOD and Caregivers of Individuals with LC-FAOD.

Respondents Reporting Education Impacts (% <i>n</i>)	Individuals with LC-FAOD who have been to school (<i>N</i> = 49)	Caregivers of individuals with LC-FAOD (<i>N</i> = 29*)	
Changed Schools	12.2%, 6	0%, 0	
Homeschooled	10.2%, 5	–	
Reduced Study Load	24.5%, 12	3.4%, 1	
Stopped/Paused Attending School	14.3%, 7	6.9%, 2	
Selected a School to Better Accommodate LC-FAOD	18.4%, 9	6.9%, 2	
Postponed/Cancelled Plans for Further Education	–	17.2%, 5	
No Impact	40.8%, 20	72.4%, 21	
Other Impact	28.6%, 14	10.3%, 3	
Reasons for Education Impacts (%<i>n</i>)	Individuals with LC-FAOD who have been to school (<i>N</i> = 49)	Caregivers of individuals with LC-FAOD (<i>N</i> = 29*)	
Hospitalizations	46.9%, 23	27.6%, 8	
ER Visits	30.6%, 15	24.1%, 7	
Outpatient Visits	30.6%, 15	27.6%, 8	
Dietary Alterations	28.6%, 14	17.2%, 5	
Physical Symptoms	40.8%, 20	24.1%, 7	
Other	12.2%, 6	0%, 0	
No Impact	40.8%, 20	72.4%, 21	
Respondents Reporting Employment Impacts (%<i>n</i>)	Individuals with LC-FAOD eligible to work (<i>N</i> = 19)	Caregivers eligible to work (<i>N</i> = 30)	
Changed Jobs	21.1%, 4	36.7%, 11	
Reduced Working Hours	57.9%, 11	33.3%, 10	
Stopped Working	21.1%, 4	36.7%, 11	
Turned Down a Job Opportunity	36.8%, 7	23.3%, 7	
Retired	0%, 0	0%, 0	
No Impact	15.8%, 3	30%, 9	
Other Impact	26.3%, 5	16.7%, 5	
Reasons for Employment Impacts (%<i>n</i>)	Individuals with LC-FAOD eligible to work (<i>N</i> = 19)	Caregivers eligible to work (<i>N</i> = 30)	
Hospitalizations	42.1%, 8	56.7%, 17	
ER Visits	31.6%, 6	46.7%, 14	
Outpatient Visits	15.8%, 3	53.3%, 16	
Dietary Alterations	5.2%, 1	26.7%, 8	
Physical Symptoms	78.9%, 15	40.0%, 12	
Other	5.2%, 1	20.0%, 6	
No Impact	15.8%, 3	30.0%, 9	
Absenteeism	Working adults living with LC-FAOD (<i>N</i> = 7)	Working caregivers of individuals with LC-FAOD (<i>N</i> = 19)	Control group
Absolute	7.9 h	9.7 h	1.9 h [‡]
Relative	6.0%	9.0%	1.2% [‡]
Presenteeism	Working adults living with LC-FAOD (<i>N</i> = 7)	Working caregivers of individuals with LC-FAOD (<i>N</i> = 19)	Control group
Absolute	74%	82%	84% [‡]
Relative	106%	105%	117% [‡]

(continued on next page)

Table 3 (continued)

Respondents Reporting Education Impacts (% , n)	Individuals with LC-FAOD who have been to school (N = 49)	Caregivers of individuals with LC-FAOD (N = 29 [*])	
Days of Work Missed Due To LC-FAOD	Working adults living with LC-FAOD (N = 7)	Working caregivers of individuals with LC-FAOD (N = 19)	Control group
In the Past 6 Months	3.3	6.2	1.4 [#]
In the Past 12 Months	5.7	10.5	2.8 [§]

Abbreviations used: LC-FAOD, long-chain fatty-acid oxidation disorders; ER, emergency room.

^{*} Caregiver responses describe the caregivers themselves, rather than the individuals with LC-FAOD. One caregiver was cleaned from the education analysis due to marking “currently in preschool” for their education status.

[†] Estimated using control group data for days of work missed, assuming an 8-h workday.

[‡] According to the National Comorbidity Survey Replication Study (NCS-R) [18].

[#] Estimated by halving BLS data on days of work missed in last 12 months.

[§] According to the United States Bureau of Labor Statistics (BLS) [19].

symptoms, with 69% of individuals with LC-FAOD considering the symptom among the top three impactful symptoms. Significantly more individuals aged 0–6 (56%) ranked hypoglycemia among the top three impactful symptoms than individuals aged 7–17 (13%, $p = 0.02$) and individuals age 18+ living with LC-FAOD (0%, $p < 0.001$). Individuals

Table 4

Comparison of Individuals with LC-FAOD by Age.

Top 5 LC-FAOD Symptoms Impacting Individual's Life (% ranked in the top 3 of 12, n)	All individuals with LC-FAOD (N = 51)	Individuals < 7 years old living with LC-FAOD (N = 16) ^(A)	Individuals 7–17 years old living with LC-FAOD (N = 15) ^(B)	Individuals 18+ years old living with LC-FAOD (N = 20) ^(C)
Muscle Weakness	69%, 35	56%, 9	73%, 11	75%, 15
Physical Fatigue	49%, 25	25%, 4	87% ^{AC} , 13	40%, 8
Rhabdomyolysis	39%, 20	19%, 3	20%, 3	70% ^{AB} , 14
Exercise Intolerance	31%, 16	19%, 3	33%, 5	40%, 8
Hypoglycemia	22%, 11	56% ^{BC} , 9	13%, 2	0%, 0
Impact on Requirements for Social Events and Rest and Relaxation; Time Spent Sitting	All individuals with LC-FAOD (N = 51)	Individuals < 7 years old living with LC-FAOD (N = 16)^(A)	Individuals 7–17 years old living with LC-FAOD (N = 15)^(B)	Individuals 18+ years old living with LC-FAOD (N = 20)^(C)
Individuals with LC-FAOD Reporting Requiring Accommodations for Social Events “Most” or “All of” the Time (% , n)	31%, 16	25%, 4	47%, 7	25%, 5
Individuals with LC-FAOD Reporting Spending “Most” or “All of” Rest/Relaxation Time Recuperating From LC-FAOD (% , n)	22%, 11	13%, 2	13%, 2	35%, 7
Average Time Spent Sitting Per Day (hours)	7.28	4.27	8.65 ^A	8.67 ^A
Difficulty Performing Everyday Activities	All individuals with LC-FAOD (% , n/N)	Individuals < 7 years old living with LC-FAOD (% , n/N)^(A)	Individuals 7–17 years old living with LC-FAOD (% , n/N)^(B)	Individuals 18+ years old living with LC-FAOD (% , n/N)^(C)
Standing/Being on Feet for Two Hours	43%, 20/47	39%, 5/13	29%, 4/14	55%, 11/20
Walking ¼ Mile	33%, 16/49	21%, 3/14	33%, 5/15	40%, 8/20
Pushing/Pulling Large Objects	32%, 14/44	10%, 1/10	33%, 5/15	42% ^A , 8/19
Lifting/Carrying Up to 10 lbs	29%, 13/45	20%, 2/10	27%, 4/15	35%, 7/20
Doing Chores Around the House	22%, 10/45	0%, 0/11	20% ^A , 3/15	37% ^A , 7/19
Analysis of WHO PAQ Instrument Responses	Individuals with LC-FAOD 18+ Years Old			
Meeting Weekly Activity Recommendations (% , n/N)	40%, 8/20			
Average METs of Age Group (METs, N)	1969, 20			
SF-12 Scoring	Control Group^(A)	Adults living with LC-FAOD^(B) (N = 14)		
Physical Component Score (PCS)	50.00 ^B	34.51		
Mental Component Score (MCS)	50.00 ^B	45.27		

Abbreviations used: LC-FAOD, long-chain fatty-acid oxidation disorders; WHO PAQ, World Health Organization Performance Activity Questionnaire

A, B, C Indicates statistical significance between indicated groups at $\alpha = 0.10$

^{*} Control data from the SF-12 was based on a representative sample of the American population and normalized to a value of 50 with a standard deviation of 10.

aged 7–17 reported physical fatigue as among the most impactful symptoms; 87% ranked it among the top three impactful symptoms – significantly more than individuals aged 0–6 (25%, $p < 0.001$) and individuals age 18+ (40%, $p = 0.006$). Individuals aged 18+ living with LC-FAOD reported rhabdomyolysis as among the top three most impactful symptoms (70%), significantly more than individuals aged 0–6 (19%, $p = 0.003$) and individuals aged 7–17 (20%, $p = 0.004$). Rankings for each symptom are shown in Supplemental Table 5.

Fourteen adults living with LC-FAOD completed the SF-12 health-related quality of life measure. When looking at physical and mental component scores (PCS and MCS), individuals with LC-FAOD reported significantly lower PCS and MCS than a control group of representative Americans (normalized to 50); the PCS was substantially lower than the MCS. Adults living with LC-FAOD reported an average PCS of 34.51 ($p < 0.001$), and an average MCS of 45.27 ($p = 0.04$). For full results, please see Table 4 and Supplemental Table 2.

3.3. LC-FAOD type comparisons

Twenty individuals were diagnosed with LCHAD, 16 with VLCAD, and 13 with CPTII. Muscle weakness was highly impactful for most individuals, regardless of type of LC-FAOD (70% of LCHAD, 63% of VLCAD, 77% of CPTII). Significantly more individuals with CPTII ranked rhabdomyolysis and hypoglycemia as highly impactful, 54% and 31% respectively when compared to individuals with LCHAD (Rhabdomyolysis: 20%, $p = 0.05$; Hypoglycemia: 5%, $p = 0.07$). Significantly more individuals with VLCAD (38%) ranked hypoglycemia as highly

impactful when compared to individuals with LCHAD (5%, $p = 0.02$).

Significantly fewer individuals with CPTII reported requiring special accommodations for social events (15%) most or all of the time than did individuals with LCHAD (45%, $p = 0.08$).

All 3 enzyme deficiencies reported significantly lower PCS, indicative of lower functioning, (LCHAD = 36.47, $p = 0.004$; VLCAD = 33.27, $p < 0.001$; CPTII = 32.71, $p < 0.001$) than the control value (50). However, only individuals with VLCAD reported significantly lower MCS (40.33, $p = 0.03$) than the control value (50), while individuals with CPTII reported significantly higher values (58.19, $p = 0.04$). For full results, please see Table 5 and Supplemental Table 3.

4. Discussion

Overall, LC-FAOD present a high burden of disease for individuals with LC-FAOD and caregivers of individuals with LC-FAOD. Due to hospitalizations, ER visits, doctor's appointments, and physical symptoms, the educational journey of these individuals is impacted, and both individuals with LC-FAOD and their caregivers often experience impacts to their employment, leading to lower-than-average subjective performance at work and higher rates of absence than average employees. Additionally, there may be variations in how individuals experience the impact of their LC-FAOD manifestations, with young children most impacted by hypoglycemia, older children most impacted by physical fatigue, and adults most impacted by rhabdomyolysis. Previously, these impacts had not been quantified in a published study. Further

investigation of findings presented here may provide an avenue to enable confirmation of results and may serve to solidify this new understanding of LC-FAOD.

Individuals with chronic illnesses face a lifetime of care. Especially for those with rare diseases, transition from pediatric to adult care can be complicated. Education and self-reflection are key to helping patients in other rare diseases, including Marfan's Syndrome [25], hemophilia [26], sickle cell disease [27], and x-linked hypophosphatemia [28], transition to self-management after childhood disease management by a caregiver. It is possible that similar access to education and counselling for individuals with LC-FAOD may improve their ability to manage the serious manifestations, mental impacts, and physical impacts of LC-FAOD not only during the transition from family-managed care, but throughout their lives.

It has been reported that individuals with LC-FAOD experience significantly lower physical QoL (according to SF-12) than a normalized control group [10], a finding that has been confirmed here. However, we have also found that individuals with LC-FAOD experience significantly lower mental QoL than the normalized control group, which differs from previously reported results [9]. Due to the disparity in results, and the low sample size of both studies ($n = 5$ previously; $n = 14$ in this study), further research may be warranted.

The mental and physical impacts of disease can have a substantial impact on patients and caregivers. Especially in rare disease [29], limited availability of information, either through the internet or through healthcare providers, may cause distress both to individuals

Table 5
Comparison of Individuals with LC-FAOD by LC-FAOD Type.

Top 5 LC-FAOD Symptoms Impacting Individual's Life (% ranked in the top 3 of 12, n)	All individuals with LC-FAOD (N = 51)*	Individuals with LCHAD (N = 20) ^(A)	Individuals with VLCAD (N = 16) ^(B)	Individuals with CPT II (N = 13) ^(C)
Muscle Weakness	69%, 35	70%, 14	63%, 10	77%, 11
Physical Fatigue	49%, 25	55%, 11	50%, 8	39%, 5
Rhabdomyolysis	39%, 20	20%, 4	44%, 7	54% ^A , 7
Exercise Intolerance	31%, 16	30%, 6	25%, 4	39%, 5
Hypoglycemia	22%, 11	5%, 1	38% ^A , 6	31% ^A , 4
Impact on Requirements for Social Events and Rest and Relaxation; Time Spent Sitting	All individuals with LC-FAOD (N = 51)*	Individuals with LCHAD (N = 20)^(A)	Individuals with VLCAD (N = 16)^(B)	Individuals with CPT II (N = 13)^(C)
Individuals with LC-FAOD Reporting Requiring Accommodations for Social Events "Most" or "All of" the Time (%, n)	31%, 16	45% ^C , 9	19%, 3	15%, 2
Individuals with LC-FAOD Reporting Spending "Most" or "All of" Rest/Relaxation Time Recuperating From LC-FAOD (%, n)	22%, 11	20%, 4	31%, 5	8%, 1
Average Time Spent Sitting Per Day (hours)	7.28	10.13 ^{BC}	5.52 ^C	4.72
Difficulty Performing Everyday Activities	All individuals with LC-FAOD (%, n/N)*	Individuals with LCHAD^(A) (%, n/N)	Individuals with VLCAD^(B) (%, n/N)	Individuals with CPTII^(C) (%, n/N)
Standing/Being on Feet for Two Hours	43%, 20/47	40%, 8/20	50%, 7/14	36%, 4/11
Walking ¼ Mile	33%, 16/49	40%, 8/20	20%, 3/15	33%, 4/12
Pushing/Pulling Large Objects	32%, 14/44	37% ^B , 7/19	9%, 1/11	42% ^B , 5/12
Lifting/Carrying Up to 10 lbs	29%, 13/45	30%, 6/20	17%, 2/12	36%, 4/11
Doing Chores Around the House	22%, 10/45	26% ^B , 5/19	0%, 0/13	36% ^B , 4/11
Analysis of WHO PAQ Instrument Responses	Individuals with LC-FAOD 18+ Years Old†	Individuals with LCHAD Age 18+	Individuals with VLCAD Age 18+	Individuals with CPT II Age 18+
Meeting Weekly Activity Recommendations (%, n/N)	40%, 8/20	14%, 1/7	40%, 2/5	71%, 5/7
Average METs of Enzyme Deficiency (METs, N)	1969, 20	1389, 7	1944, 5	2849, 7
SF-12 Scoring	Control Group^(A)	Individuals with LCHAD Age 18+ (N = 4)^(B)	Individuals with VLCAD Age 18+ (N = 4)^(C)	Individuals with CPTII Age 18+ (N = 5)^(D)
Physical Component Score (PCS)	50.00 ^{BCD}	36.47	33.27	32.71
Mental Component Score (MCS)	50.00 ^C	48.79	40.33	58.19 ^A

Abbreviations used: LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; VLCAD, very long-chain acyl-CoA dehydrogenase; CPTII, carnitine palmitoyl transferase 2; LC-FAOD, long-chain fatty-acid oxidation disorders; WHO PAQ, World Health Organization Performance Activity Questionnaire

A, B, C, D Indicates statistical significance between indicated groups at $\alpha = 0.10$

* Two individuals diagnosed with TFP and are included in the "All individuals with LC-FAOD" analysis but not in the "LC-FAOD type" analysis due to low n size

† Control data from the SF-12 was based on a representative sample of the American population and normalized to a value of 50

suffering from the disease and also to caregivers who want to be able to effectively care for their individual with LC-FAOD. Improved access to information, whether it be direct education through providers or provided in an accurate manner through the internet, is likely to provide benefits for caregivers of individuals with LC-FAOD.

Not all attributes measured had comparator or control data, limiting the potential to compare patient and caregiver results to a broader population. As data were collected through an online survey and participants were recruited from a small sample of known individuals with LC-FAOD and caregivers, participants may not be representative of the entire LC-FAOD community. Portions of the survey required a 4-week, 6-month, or 12-month recall without any pre-survey recording and may suffer from inaccuracies stemming from quickly recalling events over a long period of time. Other metrics, such as absolute and relative presenteeism, require subjective ratings of self-performance and/or the performance of others. Despite potentially introducing bias, these metrics were chosen for inclusion because they have previously shown a significant positive correlation with non-self-assessed work performance [17]. Some metrics were considered by caregivers to be non-applicable to their young children, which restricted the number of responses recorded for those metrics in younger age groups. Due to extreme rarity, individuals with CPTI and CACT enzyme deficiencies had no representation in the study. The worldwide prevalence for each is estimated to be one in one million [30].

In conclusion, LC-FAOD present a substantial impact on individuals with LC-FAOD and their caregivers due to increased difficulty encountered at school and work and sudden, debilitating symptoms that may be experienced when performing common activities.

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CRedit authorship contribution statement

Eliza Kruger: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Kristin Voorhees:** Conceptualization, Methodology, Writing – review & editing. **Nina Thomas:** Conceptualization, Methodology, Writing – review & editing. **Miller Judge:** Methodology, Formal analysis, Writing – review & editing. **John Galla:** Methodology, Formal analysis, Writing – review & editing. **Jeffrey Kung:** Methodology, Formal analysis, Writing – review & editing. **Diego Rodriguez:** Methodology, Formal analysis, Writing – review & editing.

Data availability

Due to the rarity of LC-FAOD and the small number of patients/caregivers, individual data will not be shared to safeguard privacy, consistent with the data sharing policy listed on Ultragenyx.com.

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Appendix A. Supplementary data

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