Health-Related Quality of Life and Fatigue in Children with Pompe Disease

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Objective Pompe disease is an inheritable metabolic myopathy caused by the deficiency of the lysosomal enzyme acid-α-glucosidase. The aim of this study was to investigate self-reported and parent-reported health related quality of life (HR-QOL) and fatigue in children with Pompe disease.

Study design In this cross-sectional study, the validated Child Health Questionnaire and PedsQL Multidimensional Fatigue Scale were used to respectively measure (both self-reported and parent-reported) HR-QOL and fatigue in children with Pompe disease.

Results In total, of 24 patients with Pompe disease (and their parents) participated, with a median age of 9.6 years [IQR 7.7-11.9], 14 had classic infantile Pompe disease. Self-reported HR-QOL was comparable with the healthy Dutch population on most domains, and patients with the classic infantile type scored mainly lower on physical functioning. Parents of patients with classic infantile Pompe disease reported a significantly lower HR-QOL of their children on 9 domains and parents of patients with (non-classic) childhood-onset Pompe disease on 5 domains. Self-reported fatigue levels in children with classic infantile Pompe disease were increased for 2 of 3 domains compared with healthy peers, and fatigue in patients with non-classic Pompe disease did not differ. Parents of patients with classic infantile Pompe disease reported greater levels of fatigue in all 3 domains compared with healthy children, whereas parents of children with childhood-onset disease scored greater on the cognitive fatigue domain.

Conclusions Children with Pompe disease report comparable HR-QOL on most domains compared with healthy peers. Contrarily, parent-reported HR-QOL was substantially lower on most domains compared with references values. As expected in relation to disease severity, unfavorable effects on HR-QOL and fatigue were more pronounced in patients with classic infantile Pompe disease. *(J Pediatr 2024;14:200116)*.

Pompe disease is an inheritable metabolic myopathy caused by the deficiency of the lysosomal enzyme acid-α-glucosidase (GAA).[1] The disease may present at any age. The most severe presentation of Pompe disease is the classic infantile form. These patients present shortly after birth with a hypertrophic cardiomyopathy and progressive generalized skeletal muscle weakness.[2] Without treatment, these patients die of cardiac and respiratory failure within the first year of life. Patients who are negative for cross-reactive immunological material (CRIM) do not produce any GAA protein and have a worse prognosis.[3] In the late-onset phenotype of the disease, symptoms occur later, during childhood (childhood-onset Pompe disease) or adulthood (adult-onset Pompe disease), with a more slowly progressive proximal muscle and respiratory muscle weakness. In these patients, the heart is mostly not involved.[1] In 2006, enzyme-replacement therapy (ERT) with recombinant human α-glucosidase received market authorization by the Food and Drug Administration and European Medicines Agency.[1,4] Since then, the therapy has significantly improved clinical outcomes of patients, including motor function, muscle strength, and survival.[1,3,5,6] However, ERT also has limitations, and patients may experience residual disease such as progressive muscle weakness despite ERT, which eventually may lead to wheelchair and/or ventilator dependency.[7–10] Children with classic infantile Pompe disease also may manifest orofacial-muscle weakness, dysarthria, dysphagia, hearing loss, incontinence, osteopenia, and scoliosis.[11] The hypertrophic cardiomyopathy present in infants with classic infantile Pompe disease generally responds well to therapy, although shortening of the PR interval may persist and children can manifest a delta wave, with supraventricular tachycardia occurring in a small number.[12] In addition, ERT does not cross the blood–brain barrier, leaving the brain untreated.[13] Neurocognitive development seems to be normal during the first years of life. However, over time neuroimaging shows slowly progressive white matter abnormalities in children with classic infantile Pompe disease.[13–15] Cognitive tests may show a decreased processing speed during adolescence,

CHQ	Child Health Questionnaire
CRIM	Cross-reactive immunological material
ERT	Enzyme-replacement therapy
GAA	Lysosomal enzyme acid-α-glucosidase
HRQOL	Health-related quality of life
PedsQL-MFS	PedsQL Multidimensional Fatigue Scale

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and some patients with classic-infantile type show a more generalized cognitive decline.[13,14] The brain in patients with the non-classic (milder) forms of Pompe disease up till now seems not to be affected.[16] Even so, children with childhood-onset Pompe disease may experience residual muscle weakness, which also may affect respiratory muscles.

Ultimately, these physical and cognitive impairments may result in a diminished health-related quality of life (HR-QOL) and increased levels of fatigue. Currently, there are no large studies published on HR-QOL and fatigue in children with Pompe disease. This study aimed to investigate HR-QOL and fatigue in children with Pompe disease and their parents, and compare these with healthy age-related peers. In addition, we aimed to compare outcomes of (1) children with their parents, (2) between the different phenotypes, and (1) HR-QOL scores given by mothers with those by fathers.

Methods

Patients for this cross-sectional study on HR-QOL and fatigue were recruited through the Erasmus MC–Sophia Children's Hospital, Center for Lysosomal and Metabolic Diseases, the national referral center for Pompe disease. All Dutch- or English-speaking patients in the Netherlands aged between 4 until 18 years old and their parents were contacted to participate in the study. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Erasmus MC Medical Centre (NL.70912.078.19). Pompe disease was confirmed by a demonstration of α-glucosidase-deficiency in leucocytes or fibroblasts and the identification of 2 pathogenic variants in the *GAA* gene (www.pompevariantdatabase.nl). In our center, all patients with the classic infantile phenotype receive 40 mg of ERT (alglucosidase alfa)/kg/week. All patients with the non-classic phenotype (who have started on ERT) currently receive 20 mg/kg every 2 weeks. In total 27 children with Pompe disease and 54 parents were eligible for inclusion. All parents were phoned to ask whether they wanted to participate in the study, and clear instructions were given regarding filling in the parent-reports and self-reports. The importance of giving their own answers, and thus not answering on behalf of another, was emphasized. HR-QOL and fatigue questionnaires were used as baseline measurements for a lifestyle intervention in 14 patients.[17]

Measurements

HR-QOL was measured using the widely used generic short form of the Child Health Questionnaire (CHQ), which was validated for the Netherlands.[18] The scores range from 0 to 100, and a greater score corresponds to a better HR-QOL. We used both the parent-report (CHQ-PF-28) including 28 questions and 14 domains, and the child self-report including 45 questions and 12 domains (CHQ-CF45). Data were compared with previously published data of healthy children from the Netherlands (n = 737) and their parents (n = 4538).[18–20] Fatigue was measured using the validated Dutch 18-item PedsQL Multidimensional Fatigue Scale (PedsQL-MFS). The PedsQL-MFS consists of 3 subscales: general fatigue, sleep/rest fatigue, and cognitive fatigue, and also includes a parent and child report. Scores of the PedsQL-MFS range from 0 to 100 for each subscale, with a greater score meaning less fatigue. Data were compared with the previously published norm references in health Dutch children (n = 366) and their parents (n = 497).[21]

Analysis

Data were collected in Castor (clinical Electronic Data Capture), all analyses were performed using IBM SPSS Statistics, version 25.0 (IBM Corp). Patient characteristics were described using descriptive statistics. All data were analyzed and presented as non-parametric because of the small sample size. Because of the large difference in disease burden, patients with the classic infantile type were separated from patients with the non-classic type (including patients with childhood-onset with or without cardiac involvement) in the analysis. Differences between patients with Pompe disease and their parents and healthy children and their parents were calculated using the Wilcoxon one-sample test. For all domains of the CHQ and PedsQL-MFS, an effect size including 95% CI was calculated.[22] Following the guidelines of Cohen, an effect size was considered small if <0.2, medium 0.2 to 0.5, moderate >0.5 to 0.8, and large if >0.8.[22] Differences between the patients with classic infantile type and their parents and patients with non-classic type and their parents were calculated using the 2 unrelated samples Mann-Whitney *U* test. Differences between parents was calculated using the 2 related samples Wilcoxon signed-rank test. The difference between mother, father, and child was calculated using the paired Friedman test.

Results

Patients

In total, 26 of the 27 families decided to participate in the study. One family did not respond. Two of the 26 children with Pompe disease did not fill in the questionnaire. One patient lacked cognitive skills, and 1 patient did not want to fill in the questionnaire. Nevertheless, in both cases at least 1 of the parents responded to the parental questionnaire; 51 of 54 parents filled in the questionnaires.

Fourteen included children who had classic-infantile Pompe were all treated with ERT. Median age was 9.6 years [IQR 7.7-11.9]. All had severe GAA variants; 3 patients were negative for CRIM. Six patients used walking aids, and 2 used non-invasive ventilator support (for detailed patient characteristics, see **Table**). The other 12 had the (non-classic) childhood-onset form of Pompe disease, including 2 patients with Pompe disease who received the diagnose at >1 year of age and cardiac involvement, and ranged in age from 5 to 18 years (median age 11.7 years). These patients had some residual alpha-glucosidase activity

Table. Patient characteristics

Demographics	Study population
Classic infantile, No.*	13
Age, y [IQR]	9.6 [7.7-11.9]
Female, No.	9
Age at diagnosis, mo [IQR]	3.1 [2-5.3]
Age at start of ERT, mo [IQR]	3.3 [2.1-5.5]
CRIM negative, No.	3
Use of walking aids, No.	6
Noninvasive ventilation, No.	2
Childhood-onset Pompe disease, No.†,‡	11
Age, y [IQR]	11.7 [9.2-14.9]
Female, No.	6
Patients receiving ERT, No.	9
Age at diagnosis, median, y [IQR]	3.9 [2-9.7]
Age at start of ERT, y [IQR]	4 [1.8-10.6]
Use of walking aid, No.	0
Breathing support, No.	0

Patient characteristics of included patients are detailed (children are also included in this table if only parents filled in the questionnaire).
*One child classic-infantile type did not fill in the questionnaire as he lacked cognitive skills; however, parents did fill in the questionnaire and the child was therefore included in table.
†Two patients with nonclassic disease and a late diagnosis but presented with cardiac involvement are included in the childhood-onset Pompe group.
‡One child with childhood onset did not fill in the questionnaire, as he did not want to; however, he was included in the table as his mother did fill in the questionnaire.

and were positive for CRIM. All but 3 (patients with childhood-onset) received ERT. None of the patients required walking aids or respiratory support.

HR-QOL

Children with classic infantile and childhood-onset Pompe disease self-reported comparable HR-QOL scores on most domains compared with the healthy Dutch population (**Supplement Table 1**, online; available at www.jpeds.com). Patients with the classic infantile type scored mainly lower on physical functioning and also on self-esteem and general health perceptions compared with the healthy population. Patients with the childhood-onset type only scored lower on self-esteem. When we compared patients with classic infantile Pompe disease with those with childhood-onset, only the physical functioning domain was significantly lower in patients with classic infantile Pompe disease (67 [IQR 49.6-98.2] vs 100 [91.7-100], P = .002). All CHQ outcomes, including effect sizes, can be found in **Figure**, A and **Supplement Table 2**, online; available at www.jpeds.com. Parents of patients with classic infantile type reported a significantly lower HR-QOL of their children on 9 domains (Physical Functioning, Role Physical, Bodily Pain, Mental Health, Self-Esteem, General Health Perception, Parental Impact Emotional and Time, and Family Activities), all with a large effect size. Parents of patients with the non-classic type scored HR-QOL of their children lower on 5 domains, with a large effect size (role/social: emotional, bodily pain, general health perception, parental impact emotional, and family cohesion). When we compared parent-reported HR-QOL of patients with classic infantile with patients with childhood onset, almost all domain scores were lower for patients with classic infantile (except bodily pain, behavior, and self-esteem, which did not differ significantly). Scores given by mothers and fathers did not differ on any of the domains (**Supplement Table 3** online; available at www.jpeds.com).

Fatigue

Self-reported fatigue levels in children with classic infantile Pompe disease were increased for the general fatigue and cognitive fatigue domain compared with healthy peers, with a large effect size; fatigue in those with childhood-onset Pompe did not differ (**Figure**, B and **Supplement Table 2**, online; available at www.jpeds.com). Patients with classic infantile Pompe had greater general fatigue scores compared with those with childhood-onset Pompe disease. Once again, parents gave worse scores compared with their children. Parents of children with classic infantile Pompe disease stated that their children had greater levels of fatigue in all domains compared with healthy children, whereas parents of children with childhood onset only scored greater cognitive fatigue levels, with a large effect size. Classic infantile parent-reported general fatigue levels were increased compared with those given by parents of children with childhood onset. Fatigue scores given by mothers and fathers did not differ on any of the domains.

Discussion

This study shows that patients with the classic infantile phenotype as well as those with the non-classic phenotype of Pompe disease report comparable quality of life on most domains compared with healthy peers, as well as comparing between the 2 phenotypes. However, the self-reported physical functioning domain in children with classic infantile Pompe is largely decreased compared with children with childhood-onset Pompe disease. Overall, parents, independent of the disease severity, scored their children's quality of life substantially lower than the children themselves compared with scores of parents of healthy children. Both self- and parent-reported fatigue levels in children with classic infantile Pompe disease were largely increased on most domains compared with healthy peers, whereas scores in patients with childhood-onset were comparable with healthy peers except for one domain. When we compared domain scores of mothers with fathers, all were similar.

HR-QOL

Although ERT changed the prospects of children with Pompe disease significantly, not all patients with classic infantile type who learn to walk remain able to walk, and some may need a ventilator and/or a wheelchair.[1] In contrast, some patients with childhood onset do not experience any symptoms. As ERT cannot pass the blood–brain barrier, patients with the classic infantile type might also experience white matter abnormalities resulting in cognitive impairment.[1,12] Only studies regarding the quality of life in adults with the less-

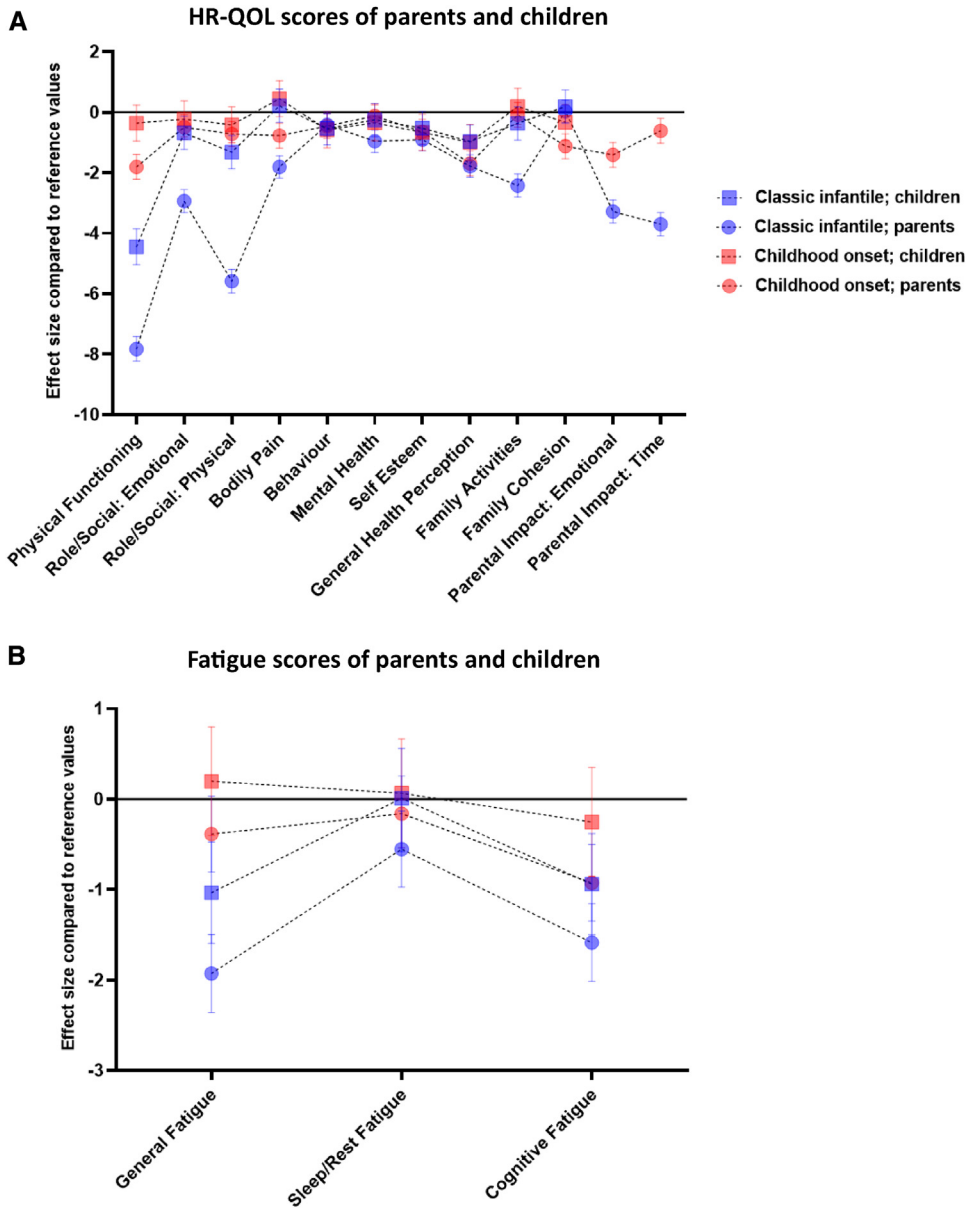

Figure. Effects size per domain of HR-QOL and fatigue in children and parents with Pompe disease as measured with, respectively, the CHQ and PedsQL-MFS. **A,** HR-QOL scores of parents and children. **B,** Fatigue scores of parents and children. Shown is the effect size per domain of both children and parents. **A,** shows quality of life as measured with the CHQ, and **B,** shows fatigue as measured with the PedsQL-MFS. *Blue* shows the patients with classic infantile type, *red* shows patients with childhood onset, *squares* are children, and *circles* represent parents.

severe form (late-onset) Pompe disease have been published.[23–25] A study including 210 (untreated) adults with Pompe disease showed primarily lower scores on physical HR-QOL, whereas patients scored only slightly lower on the mental health domains than the general population.[25] Another study in adult patients with late-onset Pompe disease showed HR-QOL greater than reference values for all domains, even before treatment, besides the domain of physical functioning, which did improve slightly after start of ERT treatment (n = 147).[24] These findings are in accordance with the self-reported findings in our patients with classic infantile Pompe disease but not with those with childhood-onset Pompe disease. Patients with classic infantile disease experience a diminished score on the physical functioning and general health domain (indicating they feel physically limited and less healthy than others). The preserved physical functioning in childhood-onset patients can be declared by the fact that most patients are (still) mildly affected. Interestingly, the only self-reported psychological health domain that was decreased (in both groups) was self-esteem.

These findings stood in large contrast to parent-reported scores of HR-QOL. The pooled results of all parents of

children with Pompe disease showed a decrease on all physical and mental domains compared with scores of parents of healthy peers. As expected, parents-reported HR-QOL of classic infantile children was lower on all almost all domains compared with the parent-reported childhood-onset scores, except for behavior (equal score) and family cohesion (greater score). This may possibly partly be explained by the age difference between the groups; patients with childhood onset were on average 3 years older, which may negatively affect behavior and family cohesion as the result of puberty.[26] Noteworthy is the significant effect of the child's disease on the family and parental impact domains. The family activities domains scored lower in both groups compared with peers, meaning that the child's health limits family activities, as was the parental impact emotional domain, meaning that parents experience great concerns regarding the health of their child. The parental impact time domain, representing limitations in time available for personal needs of parents, was only decreased in patients with the classic infantile type. This is not unusual, considering patients with classic infantile Pompe disease require more hospital visits, infusions, and are often enrolled in a special needs school. We could only identify one study investigating HR-QOL in a progressive muscle disease (Duchenne disease) using the same questionnaire, in this study parents also reported low HR-QOL on most domains.[27]

The discrepancy between the parent perception and self-reported HR-QOL, where parents tended to underestimate their children's perceived quality of life, is a known phenomenon and repeatedly found in studies of chronically ill children with various diseases, including children with Duchenne.[28–31] Various reasons might explain the disagreement, including parental concerns regarding the health of the child, disease characteristics with poorer parent-reported HR-QOL in progressive illnesses, parents' own well-being, and parental involvement in treatment and responsibility of daily care.[30] In a systematic review regarding HR-QOL in Duchenne, comparable reasons were reported as well as child-related reasons, such as reporting bias, ie, children might not be fair to doctors regarding their health; response bias, ie, relevant factors to patients' well-being are overlooked; and the fact that sick children are less likely to complain about symptoms like pain than healthy peers.[32] The utility of proxy reports in both research and clinical practice is a subject of ongoing debate. Recommendations have been made to refrain from relying on proxy reports, particularly for domains that are difficult for parents to observe, such as Mental Health and Self-Esteem.[33] However, it is noted that children often tend to provide socially desirable responses, and their assessments may be influenced by the immediate circumstances at the time of completing the questionnaire rather than reflecting longer-term experiences.[34] Conversely, some argue that the focus should not be on determining the accuracy of reports from either informant, as disparities in HR-QOL scores between informants are more indicative of differences in their perspectives. These discrepancies offer valuable insights into the dynamics of the parent-child relationship.[30]

Fatigue

Fatigue is an important feature in adults with Pompe disease, regardless of disease severity.[35] In a large international study (n = 225), 65% of the population appeared to have a fatigue severity score indicating severe fatigue.[35] Research in children with Pompe disease is lacking; however, the same fatigue questionnaire has been used in children with Duchenne disease and their parents, and they reported greater fatigue levels compared with healthy peers (child scale scores ranged between 71 and 75 and parents between 63 and 79).[36] Similarly to our population, children stated to be less fatigued compared with parents reports. In contrast to adult patients with Pompe disease, in whom fatigue seemed to be present in most patients unrelated to disease severity, in our study fatigue seemed to mainly affect patients with the classic infantile type. Children with classic infantile Pompe disease stated they had increased levels of general fatigue, reflecting feelings of overall tiredness, and cognitive fatigue, reflecting lower processing speeds, attention spans, and memory issues, compared with healthy peers. Parents agreed and also scored greater fatigue levels on the sleep/rest domain, reflecting poor sleep. Patients with childhood onset did not report greater levels of fatigue. As children with classic infantile Pompe disease show central nervous system involvement with white matter abnormalities and a decline in procession speed, this might have caused the lower score on the cognitive fatigue domain.[14] However, interestingly in this study both parents of patients with classic infantile and patients with childhood onset reported that their children had greater levels of cognitive fatigue compared with healthy peers, whereas studies investigating brain involvement in patients with nonclassic Pompe show no brain abnormalities compared with the healthy population.[14,37,38]

Clinical Implications

Measuring HR-QOL and fatigue is clinically important, as they provide crucial insights into the effect of Pompe disease on the patient's overall well-being. As these assessments offer a patient-centered perspective, this information may lead to more targeted support, including tailored (psychological) interventions and optimized patient care. In addition, HR-QOL and fatigue should be monitored over time to facilitate early detection of deteriorating overall well-being of both children and their parents, allowing for timely interventions to improve patient outcomes and quality of care. The large discrepancy between child and parent perceptions found in our study provides an opportunity to explore parental concerns, expectations, and coping mechanisms. As parents reported that the child's health limits family activities and largely affects their emotional well-being and time available for personal needs, it is advisable for clinicians to offer more additional support and resources to parents of children with Pompe disease. Tailored interventions, such as

counseling and access to support groups, might address the specific challenges faced by parents.

Strengths and Limitations

This is the first study describing HR-QOL and fatigue in children with Pompe disease. A strength of our study is that we used validated questionnaires and both self-reports and parent-reports to measure HR-QOL and fatigue from different perspectives. Although comprehensively explained to parents, we cannot verify that all children filled in their questionnaire without interference from parents. A weakness is our sample size, especially on the self-reports; however, as Pompe disease is very rare, this is a very large cohort, and we included almost all diagnosed children currently living in the Netherlands. We choose not to combine the classic infantile and childhood-onset forms, as disease severity and accompanied comorbidities and treatments differ a lot. The CHQ-CF45 and CHQ-PF28 and PedsQL-MFS are widely used and validated questionnaires in pediatric populations with various chronic diseases; however, not specifically in children with Pompe disease. Currently no other studies have investigated HR-QOL and fatigue in children with Pompe disease, we recognize the importance of future larger studies to establish the robustness and reliability of this tool in our population. In this exploratory study, we choose to report individual scales since they represent specific domains of health and well-being, such as physical functioning, rather than summary scales as research regarding quality of life in this population is very limited. We acknowledge that from a psychometrics point of view, summary scores might be preferred; however, this allowed us to gain insights into the unique challenges and strengths experienced by the children and/or parents in different aspects of their lives.

Conclusions

Surprisingly, children with Pompe disease report comparable quality of life on most domains compared with healthy peers, except for the largely decreased physical functioning domain in children with classic infantile Pompe. This is in large contrast to parent-reported HR-QOL, as they (independent of the disease severity) scored their children's quality of life substantially lower compared with scores of parents of healthy children. Fatigue levels are increased, mainly in patients with classic infantile disease. As expected in relation to disease severity, unfavorable effects were more pronounced in the patients with classic infantile Pompe and their parents. ■

CRediT authorship contribution statement

Linda E. Scheffers: Writing – original draft, Formal analysis, Conceptualization. **Karolijn Dulfer:** Writing – review & editing, Supervision. **Charlotte Lanser:** Writing – review & editing, Formal analysis. **Maarten Mackenbach:** Writing – review & editing. **Ans T. van der Ploeg:** Writing – review & editing. **Johanna M.P. van den Hout:** Writing – review & editing. **Linda E.van den Berg:** Writing – review & editing.

Declaration of Competing Interest

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Data Statement

Data sharing statement available at www.jpeds.com.

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