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Health-related quality of life in pediatric acute recurrent or chronic pancreatitis: association with biopsychosocial risk factors

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Abstract

Objectives: Abdominal pain, emergency department visits and hospitalizations impact lives of children with acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP). However, data on health-related quality of life (HRQOL) in this population remains limited. We aimed to evaluate HRQOL in children with ARP or CP; and test biopsychosocial risk factors associated with low HRQOL.

Methods: Data were acquired from the INternational Study Group of Pediatric Pancreatitis: In search for a cuRE registry. Baseline demographic and clinical questionnaires, the Child Health Questionnaire (measures HRQOL) and Child Behavior Checklist (measures emotional and behavioral functioning) were completed at enrollment.

Results: The sample included 368 children (54.3% females, mean age = 12.7 years, SD = 3.3); 65.2% had ARP and 34.8% with CP. Low physical HRQOL (M = 38.5, SD = 16.0) was demonstrated while psychosocial HRQOL (M = 49.5, SD = 10.2) was in the normative range. Multivariate regression analysis revealed that clinical levels of emotional and behavioral problems (B =−10.28, $p < .001$), episodic and constant abdominal pain (B =−4.66, $p = .03$; B =−13.25, $p < .001$) were associated with low physical HRQOL, after accounting for ARP/CP status, age, sex, exocrine and endocrine disease ($F(9, 271) = 8.34$, $p < .001$). Borderline and clinical levels of emotional and behavioral problems (B =−10.18, $p < .001$; B =−15.98, $p < .001$), and constant pain (B =−4.46, $p < .001$) were associated with low psychosocial HRQOL ($F(9, 271) = 17.18$, $p < .001$).

Conclusions: Findings highlight the importance of assessing HRQOL and treating pain and psychosocial problems in this vulnerable group of children.

Keywords

pancreatitis; quality of life; pain; emotional functioning; children

Introduction

Pediatric acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are associated with high disease burden and substantial economic costs (1–4). Abdominal pain, emergency

department consultations and hospitalizations negatively impact the lives of children with ARP and CP. In adults with ARP and CP, significantly diminished health-related quality of life (HRQOL) is well-documented (5–8). However, data on HRQOL (physical, psychological, and social functioning) in childhood ARP or CP remain limited (9–11).

Measurement of HRQOL provides valuable information to understand the disease burden of a clinical population and to evaluate the outcomes of interventions (12). Few published studies have reported on HRQOL in pediatric ARP and CP. Using the Pediatric Quality of Life Inventory, Pohl and colleagues found that children with CP (n = 38) have low HRQOL across physical, psychosocial, emotional, social and school functioning compared to healthy samples (9). Similarly, two other studies established that children's physical and psychological functioning were at almost 2 standard deviations below norms (n = 30) prior to total pancreatectomy and islet cell auto-transplantation (TPIAT) for CP (10, 11). These two studies were limited by the use of a HRQOL measure validated for adults, and only studying children with severe disease who were candidates for TPIAT. All three studies were also limited by small samples recruited from a single center. Recognizing these limitations, further data are needed to evaluate HRQOL across a larger clinical population using a tool validated in pediatric patients.

There are a number of reported risk factors associated with low HRQOL in adults with ARP and CP, including clinical features (i.e., disease severity, pain frequency), comorbidities (diabetes, cancer, cardiovascular disease), and female sex (13–16). Psychological factors such as depressive symptoms are also contributing factors (17). However, the risk factors associated with low HRQOL in children with ARP and CP are unknown. In children with other chronic health conditions, chronic pain, anxiety, depression, and behavioral problems are associated with low HRQOL (18). Understanding the relationship between HRQOL and specific risk factors may allow for improved screening methods and delivery of interventions to subgroups at risk.

The primary aim of this study was to evaluate HRQOL in children with ARP or CP. We hypothesized that children with CP would report lower HRQOL compared to children with ARP, given that a diagnosis of CP often follows a more extensive and prolonged disease course compared to ARP. Our secondary aim was to examine the relationships between biopsychosocial risk factors and low HRQOL. We hypothesized that increased age, female sex, presence of endocrine and exocrine disease, constant pain, and emotional and behavioral problems would be associated with low HRQOL.

Methods

This is a secondary analysis of data acquired from the INternational Study Group of Pediatric Pancreatitis: In search for a cuRE (INSPPIRE) in the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC). The INSPPIRE-2 study includes 22 tertiary centers from 4 countries with a current enrollment of 640 children and adolescents with ARP or CP. Information regarding INSPPIRE-2 were detailed in a previous publication (19). All centers have Institutional Review Board approval for collecting data

and met criteria of the Declaration of Helsinki. Consent was obtained from parents or guardians.

Data used in this study were obtained at the time of enrollment of children and their parents. As this was data from an international consortium, questionnaire measures were completed in the following languages, English, Spanish, French and Hebrew with translations provided by the licensing company. Baseline demographic information and medical history (e.g., information on ARP/CP, pain, comorbid medical conditions) were obtained from parent and clinician forms. Questionnaires for the assessment of HRQOL and emotional and behavioral problems were completed by parents. For the purpose of this report, our criteria for inclusion of cases were children aged 6 years to less than 18 years at enrollment, with > 50% data completion on measures of HRQOL and emotional and behavioral problems. We included data collected between July 2017 and May 2021. The only exclusion criteria was a history of TPIAT. This resulted in a final sample size of 368 participants.

Measures

Demographic and clinical factors.—Parents provided information on demographic data including age, sex, race and ethnicity. In addition, clinical data (e.g., age of diagnosis of ARP/CP, presence of pancreatic exocrine and endocrine disease (i.e., diabetes), family history, genetics, therapies and procedures were extracted from parent/child and physician questionnaires. For the purpose of the registry, ARP was defined as 2 or more episodes of acute pancreatitis occurring at least 1 month apart, with pancreatic enzymes normalization or resolution of abdominal pain between episodes. The diagnosis of CP was defined as the presence of histopathologic or imaging findings consistent of chronic pancreatic destruction, with either, abdominal pain, exocrine or endocrine pancreatic insufficiency (20).

Pain.—Parents and/or children reported on whether the child had “constant abdominal pain or abdominal pain most of the time”. The response options were “yes”, “no”, or “I don’t know”. They also reported on whether the child had “episodes of abdominal pain”. The response options were “yes”, “no”, or “I don’t know”.

Health-related quality of life.—Parents completed the Child Health Questionnaire Parent Form (CHQ-PF50; https://www.healthactchq.com). The 50 items measure 14 unique physical and psychosocial health domains: general health perceptions, physical functioning, role/social physical functioning, bodily pain, role/social emotional functioning, role/social behavioral functioning, parent impact-time, parent impact emotional, self-esteem, mental health, behavior, family activities, family cohesion, and change in health. The response time frame for most items were in the “past 4 weeks”. Items on global health asked about health “in general”, and global change items asked for “as compared to one year ago”. Scores on the items were aggregated to provide summary component physical health and psychosocial health scores, and transformed to a 0 to 100 scale with a mean ± SD of 50 ± 10; higher scores indicated higher levels of HRQOL (21). Low HRQOL has been defined as 2 standard deviations below the mean of a normative sample, or a physical or psychosocial health summary score of < 30 (22). This measure has been validated in community and clinical

samples of children and adolescents and demonstrated moderate to high internal consistency (Cronbach's alpha = 0.72) (23, 24).

Child emotional and behavioral functioning.—Parents completed the Child Behavior Checklist for Ages 6 −18 (CBCL; https://aseba.org/aseba-overview/) to assess the severity of child emotional and behavioral problems (25). This is a standardized measure with 113 items evaluating 8 syndrome scales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. Responses were rated on a 3-point scale using the timeframe of "within the last 6 months". The scales were grouped into 2 higher order factors, internalizing and externalizing problems. Internalizing problems include being anxious/depressed, withdrawn/depressed, and somatic complaints; externalizing problems combines rule-breaking and aggressive behaviors. The sum of all symptom scales provided a Total Problem score. The scores were interpreted by computing T-scores. The clinical cutoffs were defined as T < 60 as being in the "normal range", 60 – 63 as "borderline clinical range", and 64+ as having problems in the "clinical range" (26). This measure has demonstrated high test-retest reliability (Pearson's r = 0.88), internal consistency (Cronbach's alpha = 0.8), and inter-rater reliability (Pearson's r = 0.73) in nonclinical and clinical pediatric samples (27).

Statistical Analyses

Descriptive statistics were performed to summarize the demographic and clinical characteristics using mean and SD for continuous variables, and frequencies for categorical variables. To address the first aim, HRQOL (physical and psychosocial health) scores were compared between the two cohorts, ARP versus CP, using two-sample t-tests and Wilcoxon rank sum test. To address the second aim, multivariate regression analyses were used to identify predictors of physical HRQOL and psychosocial HRQOL in two separate models. Included in each of the models were disease group (ARP vs. CP), age group (6 – 10 years vs 11 – 18 years), sex (female vs. male), constant abdominal pain (yes vs. no), episodic abdominal pain (yes vs. no), and presence of exocrine or endocrine disease as independent variables. A p-value of < 0.05 was denoted as statistically significant. Participants with missing data on HRQOL within cases were omitted from these analyses (multivariate regression models). The statistical analysis was generated using SAS software version 9.4.

Results

Demographics and description of study sample

The total sample included 368 children (females = 54.3%, mean age at enrollment = 12.7 years, SD = 3.3). The majority of the children were between 11 to 18 years of age (72.6%). Over half (69.0%) identified as White, 7.1% as Black, 5.4% Asian and 18.5% of other race, with 27.7% of Hispanic ethnicity. Of the sample, 65.2% of children had a diagnosis of ARP, and 34.8% had a diagnosis of CP. Demographic and clinical characteristics of the sample are detailed in Table 1. Comparing the two cohorts of children (ARP or CP), there were no differences by age, sex, race or ethnicity. A higher proportion of children with CP had a family history and a genetic mutation compared to children with ARP (Table 1). The most common mutation was in *PRSS1*, identified more commonly in children with CP

(37.8% vs 11.7%, $p = 0.01$). In addition, a higher number of children with CP were found to have obstructive risk factors (36.8% vs 17.7%, $p < 0.001$). There were no differences on autoimmune factors, or exposure to alcohol, smoking or medications.

With regard to pharmacologic therapies, more than half of the children in both groups received medications; a higher proportion of children with CP were prescribed pancreatic enzymes, opioid and non-opioid pain medications compared to children with ARP. Concurrently, children with CP were also more likely to have procedures and surgeries compared to children with ARP (68% vs 18.3%, $p < 0.001$; 25.2% vs 12.4%, $p = 0.003$ respectively).

Pain

Across the whole sample, almost a quarter (23.6%) of children reported having constant pain, and 75.1% reported episodic pain. Constant pain was more common in children with CP (32.8%), compared to children with ARP (18.9%, $p = 0.004$). However, similar rates of episodic pain were reported by both groups (CP 74.5% vs. ARP 73.2%).

Health related quality of life

Physical HRQOL was low (Physical Health Summary Score M = 38.5, SD = 16.0) across the whole sample, while psychosocial HRQOL was in the normal range (Psychosocial Health Summary Score M = 49.5, SD = 10.2). Contrary to our hypothesis, children with ARP and CP had similar psychosocial and physical HRQOL (Table 2).

Emotional and behavioral functioning

Across the sample, 19.3% had internalizing behaviors in the clinical range; 5.2% had clinical levels of externalizing behaviors, and 11.4% had clinical levels of total scores on emotional and behavioral problems. Comparing children with ARP to children with CP, there were similar patterns of emotional and behavioral functioning (Table 2).

Multivariate associations between biopsychosocial variables and physical and psychosocial HRQOL

Multivariate regression models tested biopsychosocial predictors of physical and psychosocial HRQOL. As shown in Table 3, the model was significant for physical HRQOL ($F (9, 271) = 8.34$, $p < 0.001$, $R^2 = 0.22$). As hypothesized, clinical levels of emotional and behavioral problems (B = - 10.3, $p = 0.003$), episodic pain (B = - 4.7, $p = 0.03$) and constant pain (B = - 13.2, $p < 0.001$) were associated with low physical HRQOL, after accounting for ARP/CP status, age, sex, exocrine and endocrine disease, explaining 22% of the variance.

As shown in Table 4, the multivariate model for psychosocial HRQOL was also significant ($F (9, 271) = 17.18$, $p < 0.001$, $R^2 = 0.37$). Borderline levels of emotional and behavioral problems (B = - 10.2, $p < 0.001$), clinical levels of emotional and behavioral problems (B = - 16.0, $p < 0.001$), and constant pain (B = - 4.5, $p < 0.001$) were associated with lower psychosocial HRQOL, explaining 37% of the variance, after accounting for ARP/CP status, age, sex, exocrine and endocrine disease.

Discussion

This multi-center cohort study revealed that children with ARP or CP experienced low physical HRQOL, which includes limitations on self-care, schoolwork, or social activities, reduced general health perceptions and bodily pain. In contrast, psychosocial HRQOL (e.g., mental health, self-esteem, general behavior) was in the normative range. Contrary to our hypothesis, physical and psychosocial HRQOL scores were not different between children with ARP and CP. Emotional and behavioral functioning was also similar for children with ARP and CP; however, almost one fifth of the total cohort had clinically elevated internalizing symptoms (19%). Finally, in the multivariate models, we identified that clinical levels of emotional and behavioral problems and constant pain were consistently associated with lower physical and psychosocial HRQOL. These findings extend our current knowledge of HRQOL in children with ARP or CRP, and the associated biopsychosocial risk factors that negatively impact HRQOL.

This is the first study to compare HRQOL between children with ARP and CP. We found that children across both groups were at risk of low physical HRQOL and there were no differences between the two groups. Similar findings of low HRQOL across physical and psychological domains have been documented in adults with ARP, highlighting the importance of identifying successful therapies for this vulnerable group (5). Moreover, given the significant impact on HRQOL, future studies are needed to follow children in the early stages of disease development and understand the course of HRQOL and treatment needs.

The presence of constant pain was a significant predictor of low physical and psychological HRQOL in this study. In adults with CP and ARP, a similar association between higher pain levels and lower quality of life have been documented (5, 16, 28). The temporal pattern, specifically the constant nature of pain, has been consistently reported as an important feature negatively impacting HRQOL. To our knowledge, no studies have reported on the relationship between pain and HRQOL in children with ARP. In fact, 18.9% of children with ARP in this study reported constant pain. It is increasingly recognized that repeated painful episodes of pancreatitis may result in neural changes in the peripheral and central nervous system, akin to central sensitization processes underlying chronic pain syndromes (29). In addition to pain secondary to inflammation and nociceptive inputs, involvement of central pain pathways and pancreatic neuropathy after resolution of acute pancreatitis may perpetuate pain experiences. Given that pain is a hallmark symptom in pancreatitis, comprehensive care for both groups of children (ARP or CP) should incorporate routine pain assessment and optimization of pain management strategies (30).

Although psychosocial HRQOL was in the normative range on average in this study, a subset of children with ARP and CP had elevated emotional and behavioral problems. In particular, internalizing symptoms that include depression and anxiety were reported in 19.3% of children. Similar rates of emotional and behavioral problems have been reported in other pediatric gastrointestinal chronic illnesses (e.g., inflammatory bowel disease) (31, 32). Moreover, borderline clinical levels of symptoms were also associated with lower psychosocial HRQOL, suggesting that routine screening for subthreshold emotional and behavioral problems should be implemented during initial comprehensive evaluation and

follow-up care. Referral for psychosocial services may be indicated for children with clinical levels of internalizing symptoms. There are several strengths of this study. First, this was a multicenter study with a large cohort of children and adolescents with ARP or CP from 4 different countries. This provided a clinically relevant and diverse population, providing external validity of study findings. Second, the measures used to assess HRQOL and emotional and behavioral functioning are well validated and commonly used in pediatric chronic disease populations. This allowed comparisons of current study findings to published data from community and clinical samples.

Study findings should be interpreted in light of the following limitations. First, parents provided proxy report of children's HRQOL. Parent-child agreement on HRQOL measures have been found to vary within certain conditions, and within HRQOL domains (33). In general, parent-child agreement is higher for observable child behaviors and symptoms than for less observable, internal states (such as depressive and social withdrawal symptoms). Future studies should include child self-report using age appropriate HRQOL measures to provide the child's perspective on their HRQOL. Second, our measurement of pain was limited to an assessment of frequency (constant versus episodic). Future studies should capture additional dimensions of pain (e.g., intensity, temporal patterns, chronicity of pain) and pain interference to provide a comprehensive understanding of the relationship between pain and HRQOL (34, 35). Third, the diagnostic criteria for ARP and CP were based on histopathological or imaging findings. There is a potential for misclassification, as early-stage CP may not be detected on imaging studies. This may result in a number of children classified as ARP reporting constant pain. Longitudinal data are needed to understand the disease progression of ARP and pain. Finally, the study was limited by the cross-sectional design and single time point assessment of HRQOL and pain. Future studies using longitudinal data collection methods will advance understanding of the trajectories of HRQOL and pain over the disease course of ARP and CP.

To our knowledge, this study provides the largest dataset on HRQOL in children and adolescents with ARP or CP. Given the low physical HRQOL demonstrated by youth, it is clear that early assessment and treatment of risk factors are indicated. In particular, identification of emotional and behavioral problems and presence of chronic, disabling pain may be key factors to address low HRQOL. Currently, there are available psychosocial interventions for management of pain and treatment of poor psychosocial functioning in pediatric illnesses that may be useful for children with ARP or CP (36, 37). Moreover, pain interventions such as cognitive behavioral therapies have been implemented in other pediatric abdominal pain disorders (e.g., inflammatory bowel disease) and demonstrated to produce positive outcomes (38–40). Future research will need to evaluate whether these treatments can be applied effectively in children with ARP and CP to improve HRQOL. Finally, longitudinal data are needed to understand the trajectories of these children over time, and the impact of medical and surgical interventions on HRQOL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ARP	Acute recurrent pancreatitis
CP	Chronic pancreatitis
HRQOL	Health related quality of life
TPIAT	Total pancreatectomy and islet cell auto-transplantation
INSPPIRE	INternational Study Group of Pediatric Pancreatitis: In search for a cuRE
CPDPC	Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer's
CHQ-PF50	Child Health Questionnaire Parent Form
CBCL	Child Behavior Checklist for Ages 6 −18
ERCP	Endoscopic retrograde cholangiopancreatography

References

1. Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. J Pediatr 2015;166:890–896 e1. [PubMed: 25556020]
2. Kumar S, Ooi CY, Werlin S, A et al. Risk Factors Associated With Pediatric Acute Recurrent and Chronic Pancreatitis: Lessons From INSPPIRE. JAMA Pediatr 2016;170:562–569. [PubMed: 27064572]
3. Ting J, Wilson L, Schwarzenberg SJ, et al. Direct Costs of Acute Recurrent and Chronic Pancreatitis in Children in the INSPPIRE Registry. J Pediatr Gastroenterol Nutr 2016;62:443–449. [PubMed: 26704866]
4. Kargl S, Kienbauer M, Duba HC, et al. Therapeutic step-up strategy for management of hereditary pancreatitis in children. J Pediatr Surg 2015;50:511–514. [PubMed: 25840052]
5. Cote GA, Yadav D, Abberbock JA, et al. Recurrent Acute Pancreatitis Significantly Reduces Quality of Life Even in the Absence of Overt Chronic Pancreatitis. Am J Gastroenterol 2018;113:906–912. [PubMed: 29867178]
6. Pendharkar SA, Salt K, Plank LD, et al. Quality of life after acute pancreatitis: a systematic review and meta-analysis. Pancreas 2014;43:1194–200. [PubMed: 25333403]
7. Pezzilli R, Morselli-Labate AM, Frulloni L, et al. The quality of life in patients with chronic pancreatitis evaluated using the SF-12 questionnaire: a comparative study with the SF-36 questionnaire. Dig Liver Dis 2006;38:109–115. [PubMed: 16243011]
8. Parhiala M, Sand J, Laukkarinen J. A population-based study of chronic pancreatitis in Finland: Effects on quality of life. Pancreatology 2020;20:338–346. [PubMed: 32147309]

9. Pohl JF, Limbers CA, Kay M, et al. Health-related quality of life in pediatric patients with long-standing pancreatitis. J Pediatr Gastroenterol Nutr 2012;54:657–663. [PubMed: 22094900]
10. Bellin MD, Freeman ML, Schwarzenberg SJ, et al. Quality of life improves for pediatric patients after total pancreatectomy and islet autotransplant for chronic pancreatitis. Clin Gastroenterol Hepatol 2011;9:793–799. [PubMed: 21683160]
11. Chinnakotla S, Bellin MD, Schwarzenberg SJ, et al. Total pancreatectomy and islet autotransplantation in children for chronic pancreatitis: indication, surgical techniques, postoperative management, and long-term outcomes. Ann Surg 2014;260:56–64. [PubMed: 24509206]
12. Solans M, Pane S, Estrada MD, et al. Health-related quality of life measurement in children and adolescents: a7 systematic review of generic and disease-specific instruments. Value Health 2008;11:742–64. [PubMed: 18179668]
13. Keller CE, Wilcox CM, Gudleski GD, et al. Beyond Abdominal Pain: Pain Beliefs, Pain Affect, and Distress as Determinants of Quality of Life in Patients With Chronic Pancreatitis. J Clin Gastroenterol 2018;52:563–568. [PubMed: 28858939]
14. Olesen SS, Juel J, Nielsen AK, et al. Pain severity reduces life quality in chronic pancreatitis: Implications for design of future outcome trials. Pancreatology 2014;14:497–502. [PubMed: 25455540]
15. Pezzilli R, Morselli Labate AM, Ceciliato R, et al. Quality of life in patients with chronic pancreatitis. Dig Liver Dis 2005;37(3):181–189. [PubMed: 15888283]
16. Machicado JD, Amann ST, Anderson MA, et al. Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co-Morbidities. Am J Gastroenterol 2017;112:633–642. [PubMed: 28244497]
17. Balliet WE, Edwards-Hampton S, Borckardt JJ, et al. Depressive Symptoms, Pain, and Quality of Life among Patients with Nonalcohol-Related Chronic Pancreatitis. Pain Res Treat 2012;2012:978646. [PubMed: 23227332]
18. Seid M, Opipari L, Huang B, et al. Disease control and health-related quality of life in juvenile idiopathic arthritis. Arthritis Rheum 2009;61:393–399. [PubMed: 19248113]
19. Uc A, Perito ER, Pohl JF, et al. INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE Cohort Study: Design and Rationale for INSPPIRE 2 From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Pancreas 2018;47:1222–1228. [PubMed: 30325861]
20. Morinville VD, Husain SZ, Bai H, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. J Pediatr Gastroenterol Nutr 2012;55:261–265. [PubMed: 22357117]
21. Landgraf JM AL, Ware JE. Child Health Questionnaire (CHQ): A user's manual: Landgraf & Ware; 1999.
22. Hullmann SE, Ryan JL, Ramsey RR, et al. Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S420–30. [PubMed: 22588762]
23. Raat H, Landgraf JM, Bonsel GJ, et al. Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population. Qual Life Res 2002;11:575–581. [PubMed: 12206578]
24. J.M. L. The Child Health Questionnaire (CHQ) and psychological assessments: A brief update Adolescents TUoPTfTPaOAVIfCa, editor: Springer, Dordrecht; 2014; 443.
25. Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. Pediatr Rev 2000;21:265–271. [PubMed: 10922023]
26. TM A. The use of psychological testing for treatment planning and outcomes assessment In: ME M, editor. The Child Behavior Checklist and related instruments: Lawrence Erlbaum Associates Publishers; 1999;429–466.
27. Achenbach TMEC. Child behavior checklist. 7 Burlington (VT)1991;371–392.

28. Mullady DK, Yadav D, Amann ST, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut 2011;60:77–84. [PubMed: 21148579]

29. Olesen SS, Krauss T, Demir IE, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: mechanisms and implications for treatment. Pain Rep 2017;2:e625. [PubMed: 29392239]

30. Wilcox CM, Yadav D, Ye T, et al. Chronic pancreatitis pain pattern and severity are independent of abdominal imaging findings. Clin Gastroenterol Hepatol 2015;13:552–560; quiz e28–9. [PubMed: 25424572]

31. Mackner LM, Crandall WV. Long-term psychosocial outcomes reported by children and adolescents with inflammatory bowel disease. Am J Gastroenterol 2005;100:1386–1392. [PubMed: 15929775]

32. Szigethy E, Levy-Warren A, Whitton S, et al. Depressive symptoms and inflammatory bowel disease in children and adolescents: a cross-sectional study. J Pediatr Gastroenterol Nutr 2004;39:395–403. [PubMed: 15448431]

33. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. Qual Life Res 2008;17:895–913. [PubMed: 18521721]

34. Dampier C, Barry V, Gross HE, et al. Initial Evaluation of the Pediatric PROMIS(R) Health Domains in Children and Adolescents With Sickle Cell Disease. Pediatr Blood Cancer 2016;63:1031–1037. [PubMed: 26895143]

35. Anderson MA, Akshintala V, Albers KM, et al. Mechanism, assessment and management of pain in chronic pancreatitis: Recommendations of a multidisciplinary study group. Pancreatology 2016;16:83–94. [PubMed: 26620965]

36. Chen E, Cole SW, Kato PM. A review of empirically supported psychosocial interventions for pain and adherence outcomes in sickle cell disease. J Pediatr Psychol 2004;29:197–209. [PubMed: 15131137]

37. Lau N, Waldbaum S, Parigoris R, et al. eHealth and mHealth Psychosocial Interventions for Youths With Chronic Illnesses: Systematic Review. JMIR Pediatr Parent 2020;3:e22329. [PubMed: 33075743]

38. Levy RL, van Tilburg MA, Langer SL, et al. Effects of a Cognitive Behavioral Therapy Intervention Trial to Improve Disease Outcomes in Children with Inflammatory Bowel Disease. Inflamm Bowel Dis 2016;22:2134–2148. [PubMed: 27542131]

39. Abbott RA, Martin AE, Newlove-Delgado TV, et al. Psychosocial interventions for recurrent abdominal pain in childhood. Cochrane Database Syst Rev 2017;1:CD010971. [PubMed: 28072460]

40. Rich KL, Abu-El-Haija M, Nathan JD, et al. The Role of Psychology in the Care of Children With Pancreatitis. Pancreas 2020;49:887–890. [PubMed: 32675785]

What is Known

- Pediatric acute recurrent pancreatitis and chronic pancreatitis are associated with high disease burden and substantial economic costs.
- Low health-related quality of life is well-documented in adults with acute recurrent pancreatitis and chronic pancreatitis; however, data in children are limited.
- Pain, emotional and behavioral problems are associated with low health-related quality of life in other pediatric chronic health conditions, raising questions whether these risk factors similarly impact children with acute recurrent pancreatitis or chronic pancreatitis.

What Is New

- Both children with acute recurrent pancreatitis or chronic pancreatitis were similarly at risk for low physical health-related quality of life.
- Almost one fifth of the children with acute recurrent pancreatitis or chronic pancreatitis reported clinical levels of internalizing symptoms (e.g., anxiety, depression, social withdrawal).
- The presence of constant pain, emotional and behavioral problems were associated with low health-related quality of life across both physical and psychosocial domains in children with acute recurrent or chronic pancreatitis.

Table 1.

Demographic and clinical variables for children with ARP and CP[a]

Demographics		**ALL (N = 368)**	**ARP (n = 240)**	**CP (n = 128)**	***p***
Age at enrollment, mean (SD), years		12.7 (3.3)	12.7 (3.2)	12.6 (3.5)	0.99
Female, No. (%)		200 (54.3)	122 (50.8)	78 (60.9)	0.06
Race, No. (%)	White	254 (69.0)	169 (70.4)	85 (66.4)	0.30
	Black	26 (7.1)	17 (7.1)	9 (7.0)	
	Asian	20 (5.4)	9 (3.8)	11 (8.6)	
	Other	68 (18.5)	45 (18.8)	23 (18.0)	
Hispanic, No. (%)		102 (27.7)	67 (27.9)	35 (27.3)	1.00
Constant abdominal pain, No. (%)		81/343 (23.6)	43/227 (18.9)	38/116 (32.8)	**0.004**
Episodes of abdominal pain, No. (%)		256/341 (75.1)	168/223 (75.3)	88/113 (74.6)	0.88
Risk Factors, No. (%)					
Family history of CP		67/319 (21.0)	30/208 (14.4)	37/111 (33.3)	< **0.001**
Genetic mutations		175/364 (48.1 %)	102/237 (43.0 %)	73/127 (57.5 %)	**0.01**
	CFTR	81/249 (32.5 %)	59/156 (37.8 %)	22/93 (23.7 %)	**0.03**
	SPINK1	58/242 (24.0 %)	39/149 (26.2 %)	19/93 (20.4 %)	0.35
	PRSS1	55/252 (21.8 %)	18/154 (11.7 %)	37/98 (37.8 %)	< **0.001**
	CTRC	16/188 (8.5 %)	9/122 (7.4 %)	7/66 (10.6 %)	0.58
Obstructive		87/357 (24.4 %)	41/232 (17.7 %)	46/125 (36.8 %)	< **0.001**
	Pancreas divisum	35/86 (40.7 %)	13/40 (32.5 %)	22 /46(47.8 %)	0.19
	Gallstones	14/87 (16.1 %)	6/41 (14.6 %)	8/46 (17.4 %)	0.78
	Pancreaticobiliary malunion	8/86 (9.3 %)	5/40 (12.5 %)	3/46 (6.5 %)	0.46
	Choledochal cyst	7/84 (8.3 %)	4/40 (10.0 %)	3/44 (6.8 %)	0.70
	Duct obstruction	6/86 (7.0 %)	0/40 (0.0 %)	6/46 (13.0 %)	**0.03**
	Annular pancreas	3/86 (3.5 %)	1/40 (2.5 %)	2/46 (4.3 %)	> 0.99
	Other	15/89 (16.9 %)	5/43 (11.6 %)	10/46 (21.7 %)	0.26
Autoimmune		33/364 (9.1 %)	22/237 (9.3 %)	11/127 (8.7 %)	> 0.99
	Autoimmune pancreatitis	7/347 (2.0 %)	2/226 (0.9 %)	5/121 (4.1 %)	0.05

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Demographics	ALL (N = 368)	ARP (n = 240)	CP (n = 128)	*p*
Celiac disease	5/33 (15.2 %)	4/24 (16.7 %)	1/9 (11.1 %)	> 0.99
Crohn's Disease	4/31 (12.9 %)	4/22 (18.2 %)	0/9 (0.0 %)	0.30
Autoimmune hepatitis	4/33 (12.1 %)	1/24 (4.2 %)	3/9 (33.3 %)	0.05
Ulcerative colitis	3/30 (10.0 %)	3/21 (14.3 %)	0/9 (0.0 %)	0.53
Other	30/358 (8.4 %)	21/232 (9.1 %)	9/126 (7.1 %)	0.69
Medication-related	26/356 (7.3 %)	21/233 (9.0 %)	5/123 (4.1 %)	0.13
Passive smoking exposure	22/311 (7.1 %)	15/202 (7.4 %)	7/109 (6.4 %)	0.82
Alcohol use	3/360 (0.8 %)	3/235 (1.3 %)	0/125 (0.0 %)	0.55
Active smoking	1/358 (0.3 %)	1/232 (0.4 %)	0 /126(0.0 %)	> 0.99
Pharmacologic Therapies				
Any medications	235/352 (66.8 %)	137/227 (60.4 %)	98/125 (78.4 %)	< **0.001**
Pancreatic enzymes	111/349 (31.8 %)	53/227 (23.3 %)	58/122 (47.5 %)	< **0.001**
Vitamins/anti-oxidants	105/358 (29.3 %)	62/234 (26.5 %)	43/124 (34.7 %)	0.11
Pain medications	132/345 (38.3 %)	69/227 (30.4 %)	63/118 (53.4 %)	< **0.001**
Opioids	5/345 (1.4 %)	1/227 (0.4 %)	4/118 (3.4 %)	**0.05**
Diabetes medications	30/362 (8.3 %)	18/234 (7.7 %)	12/128 (9.4 %)	0.56
Steroids	7/353 (2.0 %)	4/231 (1.7 %)	3/122 (2.5 %)	0.70
Procedures				
Any ERCP[d] procedure	131/368 (35.6 %)	44/240 (18.3 %)	87/128 (68.0 %)	< **0.001**
Pancreatic stent placement	89/127 (70.1 %)	27/42 (64.3 %)	62/85 (72.9 %)	0.41
Pancreatic stricture dilation	83/124 (66.9 %)	26/84 (65.0 %)	57/40 (67.9 %)	0.84
Pancreatic sphincterotomy	83/124 (66.9 %)	26/40 (65.0 %)	57/84 (67.9 %)	0.83
Biliary stricture dilation	48/124 (38.7 %)	18/42 (42.9 %)	30/82 (36.6 %)	0.56
Biliary sphincterotomy	48/124 (38.7 %)	18/42 (42.9 %)	30/82 (36.6 %)	0.56
Biliary stent placement	18/123 (14.6 %)	5/81 (11.9 %)	13/42 (16.0 %)	0.60
Biliary stone extraction	6/123 (4.9 %)	2/41 (4.9 %)	4/82 (4.9 %)	> 0.99
Cystogastrostomy	1/99 (1.0 %)	0/68 (0.0 %)	1/31 (1.5 %)	> 0.99
Other interventions	42/124 (33.9 %)	7/41 (17.1 %)	35/83 (42.2 %)	**0.01**

Demographics	ALL (N = 368)	ARP (n = 240)	CP (n = 128)	*p*
Surgical therapy	61/360 (16.9 %)	29/233 (12.4 %)	32/127 (25.2 %)	**0.003**
Cholecystectomy	40/70 (57.1 %)	23/32 (71.9 %)	17/38 (44.7 %)	**0.02**
Partial pancreatectomy	9/71 (12.7 %)	3/34 (8.8 %)	6/37 (16.2 %)	0.48
Lateral pancreaticojejunostomy	9/72 (12.5 %)	2/34 (5.9 %)	7/38 (18.4 %)	0.16
Cyst/pseudocyst operation	7/72 (9.7 %)	4/34 (11.8 %)	3/38 (7.9 %)	0.70

[a] Participants with TPIAT were excluded from study analyses.

[b] Percentages are based on the total number of responses for each variable as the number of missing data and invalid responses were different for each variable.

[c] IBD = Inflammatory bowel disease

[d] ERCP = Endoscopic retrograde cholangiopancreatography

Table 2.

Physical HRQOL, psychosocial HRQOL, emotional and behavioral functioning in children with ARP and CP

HRQOL		ALL (N = 313) M (SD)	ARP (N = 212) M (SD)	CP (N = 101) M (SD)	*p*
Physical Health		38.5 (16.0)	39.8 (14.9)	36.0 (17.7)	0.10
Psychosocial Health		49.5 (10.2)	49.7 (10.0)	49.0 (10.5)	0.66
		n (%)	**n (%)**	**n (%)**	
Emotional and behavioral functioning: Total score	Normal range	293 (79.6)	195 (81.3)	98 (76.6)	0.52
	Borderline Clinical range	33 (9.0)	19 (7.9)	14 (10.9)	
	Clinical range	42 (11.4)	26 (10.8)	16 (12.5)	
Emotional and behavioral functioning: Internalizing symptoms	Normal range	258 (70.1)	169 (70.4)	89 (69.5)	0.88
	Borderline Clinical range	39 (10.6)	24 (10)	15 (11.7)	
	Clinical range	71 (19.3)	47 (19.6)	24 (18.8)	
Emotional and behavioral functioning: Externalizing symptoms	Normal range	333 (90.5)	215 (89.6)	118 (92.2)	0.78
	Borderline Clinical range	16 (4.3)	11 (4.6)	5 (3.9)	
	Clinical range	19 (5.2)	14 (5.8)	5 (3.9)	

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Table 3:

Multiple regression analysis predicting physical HRQOL (n = 272 *)

Effect		Estimate	Standardized Estimate	Standard Error	*p*
Intercept		47.93	0	2.54	**<.0001**
Emotional and behavioral problems	Borderline Clinical range	− 4.86	− 0.09	2.94	0.10
	Clinical range	− 10.28	− 0.20	2.80	**< 0.001**
Diagnoses of CP		− 1.54	− 0.05	2.03	0.45
Age: 11 to 18 years		− 0.21	− 0.01	2.09	0.92
Sex: Female		− 1.41	− 0.04	1.89	0.46
Constant abdominal pain		− 13.25	− 0.35	2.17	**<.0001**
Episodic abdominal pain		− 4.66	− 0.12	2.09	**0.03**
Exocrine disease		− 1.34	− 0.03	2.48	0.59
Endocrine disease		− 1.57	− 0.02	4.00	0.69

*Sample size for analyses included participants with all available data in the model.

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Table 4:

Multiple regression analysis predicting psychosocial HRQOL (n = 272*)

Effect		Estimate	Standardized Estimate	Standard Error	*p*
Intercept		55.24	0	1.46	**<.0001**
Emotional and behavioral problems	Borderline Clinic range	− 10.18	− 0.30	1.69	**<.0001**
	Clinical range	− 15.98	− 0.49	1.61	**<.0001**
Diagnosis of CP		0.59	0.03	1.17	0.34
Age: 11 to 18 years		− 1.57	− 0.07	1.20	0.13
Sex: Female		0.55	0.03	1.09	0.62
Constant abdominal pain		− 4.46	− 0.18	1.25	**<0.001**
Episodic abdominal pain		− 1.61	− 0.07	1.20	0.18
Exocrine disease		− 2.02	− 0.08	1.42	0.16
Endocrine disease		− 2.29	− 0.05	2.30	0.32

*Sample size for analyses included participants with all available data in the model

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