



Published in final edited form as:

*Clin Gastroenterol Hepatol.* 2023 July ; 21(7): 1781–1791.e4. doi:10.1016/j.cgh.2022.09.026.

## ASSOCIATION OF CHRONIC PANCREATITIS PAIN FEATURES WITH PHYSICAL, MENTAL AND SOCIAL HEALTH

Dhiraj Yadav, MD MPH<sup>1</sup>, Robert L. Askew, PhD<sup>2</sup>, Tonya Palermo, PhD<sup>3</sup>, Liang Li, PhD<sup>4</sup>, Dana K. Andersen, MD<sup>5</sup>, Minxing Chen, MS<sup>4</sup>, William E. Fisher, MD<sup>6</sup>, Evan L. Fogel, MD MSc<sup>7</sup>, Christopher E. Forsmark, MD<sup>8</sup>, Phil A. Hart, MD<sup>9</sup>, Mohamed O. Othman, MD<sup>10</sup>, Stephen J. Pandol, MD<sup>11</sup>, Walter G. Park, MD<sup>12</sup>, Mark D. Topazian, MD<sup>13</sup>, Stephen K. Van Den Eeden, PhD<sup>14</sup>, Santhi Swaroop Vege, MD<sup>13</sup>, Yunlong Yang, PhD<sup>4</sup>, Jose Serrano, MD, PhD<sup>5</sup>, Darwin L. Conwell, MD MSc<sup>9</sup> Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)

<sup>1</sup>Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA

<sup>2</sup>Department of Psychology, Stetson University, DeLand, FL

<sup>3</sup>Department of Anesthesiology, University of Washington, Seattle, WA

<sup>4</sup>Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX

<sup>5</sup>Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

<sup>6</sup>Division of General Surgery, Baylor College of Medicine, Houston, TX

<sup>7</sup>Digestive and Liver Disorders, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

<sup>8</sup>Division of Gastroenterology, Hepatology, and Nutrition. University of Florida, Gainesville, FL

**Address correspondence to:** Dhiraj Yadav, MD, MPH, Professor of Medicine, Division of Gastroenterology & Hepatology, University of Pittsburgh Medical Center, 200 Lothrop Street, M2, C-wing, Pittsburgh, PA 15213, yadavd@upmc.edu, Tel: 412 648 9825 Fax: 412 383 8992.

Author contributions:

Conceptualization: DY, RLA, TP, LL, PAH, YY, DLC

Funding acquisition: DY, WEF, ELF, CEF, PAH, SJP, WGP, MDT, SKV, SSV, DLC

Methodology: DY, RLA, TP, DKA, MC, WEF, ELF, CEF, PAH, MOO, SJP, WGP, MDT, SKV, SSV, YY, JS, DLC

Data curation: LL, MC, YY

Formal analysis: LL, MC, YY

Project administration: DY, LL, DKA, JS, DLC

Supervision: DY, LL, DKA, JS, DLC

Writing original draft: DY, RLA, TP, LL, PAH, DLC

Writing – review and editing: All authors

Recruitment: DY, WEF, ELF, CEF, PAH, MOO, SJP, WGP, MDT, SKV, SSV, DLC

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Conflict of Interest:** The authors declare no relevant conflicts.

Data from this study were presented in part at the American Gastroenterological Association's Annual Meeting, Digestive Diseases Week May 2020 and May 2022.

<sup>9</sup>Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH

<sup>10</sup>Gastroenterology & Hepatology Section, Baylor College of Medicine, Houston, TX

<sup>11</sup>Division of Digestive and Liver Diseases, Cedars-Sinai Medical Center, Los Angeles, CA

<sup>12</sup>Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA

<sup>13</sup>Division of Gastroenterology & Hepatology, Mayo Clinic, Rochester, MN

<sup>14</sup>Division of Research, Kaiser Permanente Northern California, Oakland, CA

## Abstract

**Introduction.**—Pain is a cardinal symptom of chronic pancreatitis (CP). Using PROMIS measures, we characterized physical and mental health and symptom profiles of a well-defined cohort of individuals with CP and compared them to controls. Among patients with CP, we also examined associations between pain (intensity, temporal nature) and PROMIS symptom profiles and the prevalence of clinically significant psychological comorbidities.

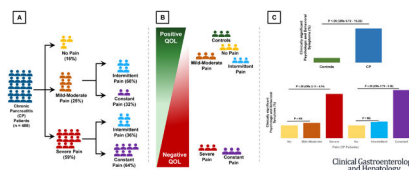
**Methods.**—We analyzed baseline data in 488 CP patients and 254 controls enrolled in PROCEED, an ongoing longitudinal cohort study. Participants completed the PROMIS-Global Health, which captures global physical and mental health, and the PROMIS-29 profile which captures seven symptom domains. Self-reported pain was categorized by severity (none, mild-moderate, severe) and temporal nature (none, intermittent, constant). Demographic and clinical data were obtained from the PROCEED database.

**Results.**—Pain was significantly associated with impairments in physical and mental health. Compared with participants with no pain, CP participants with severe pain (but not mild-moderate pain) had more decrements in each PROMIS domain in multivariable models (effect sizes: 2.54–7.03), and higher prevalence of clinically significant depression, anxiety, sleep disturbance and physical disability (odds ratios, ORs: 2.11–4.74). Similar results were noted for constant pain (but not intermittent pain) for PROMIS domains (effect sizes: 4.08–10.37), and clinically significant depression, anxiety, sleep disturbance and physical disability (ORs: 2.80–5.38).

**Conclusions.**—Severe and constant pain are major drivers for poor psychological and physical health in CP. Systematic evaluation and management of psychiatric comorbidities and sleep disturbance should be incorporated into routine management of patients with CP.

[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03099850) number-NCT03099850.

## Graphical Abstract



## Keywords

pancreatitis; PROMIS; depression; anxiety; sleep disturbance; pancreas

---

## INTRODUCTION.

Abdominal pain is common symptom (~90%) in patients with chronic pancreatitis (CP) that can be debilitating and difficult to treat<sup>1</sup>. Opioid medications are frequently used for managing pain<sup>1</sup>, but too often lead to dependence and side effects. While treatments such as endoscopic and surgical therapies provide durable pain relief in a subset, many patients continue to live with chronic daily pain<sup>1, 2</sup>. As a result, pain remains the most frequent reason for inpatient and outpatient care<sup>1</sup>.

Prior studies have demonstrated that constant pain (vs. intermittent pain) in CP is associated with higher pain severity, greater use of opioids, and lower quality of life (QOL)<sup>2</sup>. For example, in one recent study, constant pain, use of opioids, and alcohol etiology were associated with low QOL, but these variables accounted for a small amount of overall variance<sup>3</sup>. Psychological and behavioral comorbidities are common in individuals with chronic pain conditions<sup>4, 5</sup>, including CP<sup>6</sup>. Psychological comorbidities can also be sustained by ongoing pain, which has been shown to exacerbate symptoms of anxiety, depression, and sleep disturbance, resulting in a mutually maintaining effect<sup>7-9</sup>. Studies investigating psychologic comorbidities in patients with CP have found that patients with anxiety or depression reported higher pain prevalence, pain severity and pain interference as well as reduced global health and QOL<sup>6</sup>. However, the broader prevalence of these and related psychological and behavioral comorbidities, like sleep disturbance and social functioning has not been examined in CP. Sleep quality and fatigue are highly associated with pain and disability in other conditions,<sup>4, 5, 8</sup> and this represents an important knowledge gap in CP.

Using a cross-sectional analysis of an ongoing cohort study, our aims were to: 1) compare global health and symptom profiles using Patient Reported Outcome Measurement Information System (PROMIS) measures, specifically Global health, Anxiety, Depression, Sleep Disturbance, Pain Interference, Fatigue, Physical Function, and Social Role Participation in patients with CP and a healthy comparison group; 2) among patients with CP, examine associations between pain (intensity, temporal nature) and PROMIS symptom profiles; and 3) among patients with CP, examine associations between pain (intensity, temporal nature) and the prevalence of clinically significant psychological and behavioral comorbidities. Based on prior literature, we hypothesized that patients with CP would have worse global health and symptom profiles compared to the control group. Within the CP group, we hypothesized that more intense pain or constant pain would be associated with worse global health and higher rate of clinically significant psychological comorbidities<sup>10</sup>.

## METHODS.

### Study population

We analyzed data from Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED), an ongoing, multicenter, prospective longitudinal cohort study of CP in the United States (NCT03099850), sponsored by the National Institutes of Health (NIH)<sup>11</sup>. The study was approved by the Institutional Review Boards of each of the participating institutions and the Coordinating and Data Management Center. Informed consent was provided by participants before any study procedures.

The current analysis included 488 participants with definite CP and 254 controls without pancreatic disease enrolled from June 2017 to May 2020 who completed PROMIS measures. CP was defined by the presence of Cambridge stage 3–4 findings or pancreatic parenchymal or ductal stones on cross-sectional imaging or histologic evidence of CP<sup>11</sup>. A designated radiologist at each institution reviewed imaging studies according to a standardized protocol<sup>12</sup>, which has been demonstrated to achieve a high level of concordance for cohort assignment<sup>13</sup>. Selection and eligibility for control subjects is reported in Supplementary Data.

### Clinical data

Detailed demographic and clinical data were prospectively collected from participants using standardized questionnaires and from physicians using structured case report forms. Participants with CP indicated if they experienced abdominal pain related to pancreatitis in the year preceding enrollment. Those with a positive response provided information on the severity and temporal nature of pain using five predefined choices, which were used to categorize participants based on pain severity (no pain, mild-moderate pain, severe pain) and temporal nature (no pain, intermittent pain, constant pain) as previously reported<sup>14</sup>.

### PROMIS measures

PROMIS is an NIH-funded initiative which has developed valid and precise measures for approximately 70 distinct health domains that can be used without a contract and is available free of charge<sup>15</sup>. PROMIS measures employ a T-score metric that is anchored to the estimated U.S. general population mean of 50 (SD=10), such that individual scores are not only comparable across distinct clinical populations through a common reference point, but are also readily interpretable as percentiles in a normal distribution. A substantial body of evidence documents the validity and reliability of the PROMIS measures across diverse clinical populations<sup>16</sup>.

At enrollment, the PROMIS Global Health Version 1.2 and PROMIS-29 Profile Version 2.0 instruments were self-administered to study participants via paper questionnaires. The PROMIS Global Health instrument consists of 10 questions, the responses to which are used to generate physical and mental component scores. The PROMIS-29 instrument consists of 29 questions which assess subdomains of Anxiety, Depression, Sleep Disturbance, Pain Interference, Fatigue, Physical Function, and Social Role Participation<sup>17</sup>. Response options

range from 1–5 (e.g., Never/Not at all to Always/Very much), and raw sum scores are calculated by adding together responses to all items within a domain.

### Statistical Procedures

For each domain (two for PROMIS Global health, seven for PROMIS 29), T-scores were calculated using sum score to T-score tables according to recommended protocols<sup>17</sup>. From PROMIS 29 scores, we calculated the percentage of participants who had clinically relevant symptoms (moderate-severe symptoms) using recommended cut points of  $T > 60$  for negatively worded concepts (high or very high anxiety, depression, sleep disturbance) and  $T < 40$  for positively worded concepts (low or very-low physical function)<sup>18</sup>. T-scores for the domains, and percentage of participants with moderate-severe symptoms of depression, anxiety, sleep disturbance, and low physical function were compared between participants with CP and controls, and again within the CP cohort after stratification by severity and temporal nature of pain.

One-way ANOVAs, t-tests, or Chi-squared tests were applied to examine the between group difference on continuous and categorical outcomes respectively. Mean differences or odds ratios (OR) were calculated as appropriate, with 95% confidence intervals. Cohen's *d* was used to estimate effect sizes. Ordinary least squares regression was applied to examine the independent association of CP (versus controls) with each of the nine PROMIS domains separately, adjusting for demographic and clinical covariates (age, sex, race, ethnicity, body mass index [BMI], education, marital status, employment status, income, current smoking and drinking). Similar regressions were then applied to the CP cohort to examine the adjusted effects of differing level of pain severity as well as temporal nature of pain, controlling for these and additional covariates (alcohol etiology, diabetes, exocrine dysfunction, calcifications on imaging studies, pancreatitis duration, prior endoscopic treatment, surgery and Charlson comorbidity index). Standard model diagnostics were used to ensure proper model fit. There were sporadic missing data in covariates. Mean (for continuous covariates) or mode (for categorical covariates) imputation was used when there were fewer than 10 missing values; for categorical variables with 10 or more missing values (e.g., annual income), a separate category was created and included in the model for adjustment. The study used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies.<sup>19</sup>

## RESULTS.

### Participants

When compared with controls, participants with CP were significantly older, more likely to be white, non-Hispanic, have a low or normal BMI, current cigarette smokers and less likely to be current drinkers (Table 1). Significant differences were also noted in education, employment and income with the CP group having lower socioeconomic indicators than the control group. Alcohol was attributed as the primary etiology for CP in 42.5% participants, 43.6% had diabetes, 42.4% had exocrine pancreatic dysfunction, and 73.8% had calcifications. Abdominal pain in the preceding year was reported by 84% participants with CP, over half rated their pain as severe (58.6%), and 45.7% as constant (Table 1).

## Global Health and Symptom Profiles in CP vs. controls

As hypothesized, participants with CP had significantly lower global health than controls with larger differences observed in Global Physical Health and Global Mental Health representing 1.2 and 0.8 standard deviations difference, respectively (eTable 2). Similarly, on univariate analysis, participants with CP had significant impairment in each of the physical, mental, and social health domains that comprise the PROMIS 29 profile (all  $p < 0.001$ , Cohen's  $d$  range: 0.88–2.10) as shown in Figure 1 and Supplementary Table 1.

In adjusted regression analyses, the presence of CP was independently associated with a reduction of 7.15 points in PROMIS Global Physical Health and 3.13 points in Global Mental Health ( $p < 0.001$ ). With respect to PROMIS 29 symptom profiles, significant differences were observed in participants with CP compared to controls (range=2.95–7.01 points) with the largest differences in fatigue, followed by pain interference, sleep disturbance, social roles, physical function, anxiety and depression (Table 2). Notably, across all domains, between 24–52% of the variance in QOL scores was explained by CP and relevant covariates included in the models.

## Associations of Pain Severity and Temporality with Physical, Mental, and Social Health in CP

Regarding Global Health and the PROMIS 29, progressively larger differences were noted between the no pain, mild-moderate, and severe pain categories (Figure 1 and Supplementary Table 2). Adjusted comparisons from multivariable regression models indicated that differences between the no pain and the mild-moderate pain groups were not significant (Table 3). In contrast, large decrements were observed for participants with severe pain with the largest in pain interference ( $60.9 \pm 10.3$ ), fatigue ( $56.5 \pm 10.0$ ), and physical function ( $43.8 \pm 9.3$ ). Adjusted comparisons from multivariable regression models indicated significant effects of severe pain (vs. no pain group) in all PROMIS domains (range: 2.54–7.03 points).

Summary scores for PROMIS Global Health and the PROMIS 29 also differed based on temporality of pain (Figure 1 and Supplementary Table 2). Adjusted estimates from multivariable regression models indicated that differences between the no pain and the intermittent pain groups were not significant (Table 3). However, large deficits were observed for those in the constant pain group in Global Physical Health ( $37.6 \pm 7.2$ ), Global Mental Health ( $42.7 \pm 8.7$ ), and each of the PROMIS-29 domains, with the largest in pain interference ( $64.1 \pm 8.4$ ), fatigue ( $59.1 \pm 9.2$ ), and physical function ( $41.6 \pm 8.7$ ). Adjusted effects of constant pain (vs. no pain group) from multivariable regression models were statistically significant for all PROMIS domains (range: 4.08–10.37).

## Prevalence of moderate-severe symptoms of depression, anxiety, problematic sleep, and low physical function

A significantly higher proportion of participants with CP (vs. controls, all  $p < 0.001$ ) met or exceeded thresholds indicative of moderate-severe symptoms of depression, anxiety, sleep disturbance, and low physical function (range of ORs 9.92–19.36) (Figure 2, Supplementary Table 3). Comparisons among CP subgroups indicated that rates of clinically significant

comorbidities in participants with no pain were not statistically significant from participants with mild-moderate pain (range of ORs: 0.83–1.62, all  $p > 0.05$ ), and those with intermittent pain (range of ORs: 0.81–1.44, all  $p > 0.05$ ). In contrast, when compared with participants with no pain, the rate of comorbidities was between 2.11–4.74 times greater in participants with CP who had severe pain and between 2.79–5.38 times greater in participants with CP who had constant pain (Figure 2, Supplementary Table 4); these results are statistically significant at 0.05 level as the 95% confidence intervals did not cover 1.

## DISCUSSION.

To our knowledge, this is the first study to use PROMIS profile measures to characterize physical, mental, and social health in patients with CP. We noted significant decrements in all PROMIS domains in patients with CP when compared to controls. We found that presence of either severe or constant pain was a major factor associated with reduction in global health and all symptom domains. A sizeable subgroup of patients with CP demonstrated clinically significant psychological and behavioral comorbidities including anxiety, depression, sleep disturbance, and physical disability, with the highest rates among patients with either severe or constant pain. Our findings support ongoing research into the effective management of pain in CP, as well as the need for a broader approach to incorporate evaluation and treatment of psychological and behavioral comorbidities.

We observed a dose-response relationship between pain and decrement in health status such that patients with no, mild-moderate, and intermittent pain have little impairment while those with severe or constant pain had significant impairments. As a group, patients with CP reported significantly greater psychological and behavioral comorbidities than controls. Raw and adjusted differences in physical, mental, and social health between controls and CP consistently exceeded and often doubled or tripled validated thresholds of minimal clinically important differences in PROMIS measures<sup>20</sup>. However the largest drivers of differences in health status and prevalence estimates of clinically significant psychological and behavioral comorbidities in CP were severe pain and constant pain, suggesting the sustained effect of ongoing pain on health status is greater than intermittent disruptions. As observed in multiple patient populations<sup>21</sup>, chronic pain can become increasingly complex over time in its pathophysiology, maintaining psychosocial and functional consequences and compounding costs to patients, making pain more difficult to manage.

In the absence of local complications, patients with significant burden of abdominal pain symptoms who have pancreatic duct obstruction from stones and/or strictures often undergo endoscopic and/or surgical treatment. However, a durable response even with invasive therapies is suboptimal. Although psychological comorbidities in patients with CP are recognized<sup>6</sup>, systematic evaluation and management of anxiety, depression and sleep disturbance as part of pain management has not been included in treatment guidelines for pain in CP<sup>22, 23</sup>. In other chronic pain populations, cognitive-behavioral treatments have been developed to address anxiety, depression, and sleep problems finding positive effects for reducing pain interference<sup>24</sup>. In particular, treatment of comorbid sleep disturbance has been identified as an important aspect of chronic pain management where cognitive-behavioral therapy for insomnia has produced positive effects on pain

reduction<sup>25, 26</sup>. Whether treatment of these comorbid factors leads to improved outcomes of pain management has not been systematically evaluated in CP. Our data show a high prevalence of psychological comorbidities and sleep problems, especially in patients with significant symptom burden, suggesting that a multidisciplinary approach to address these factors should be included in the treatment algorithm for management of pain in patients with CP.

In prior studies of QOL using SF12, demographics, risk factors, and disease-specific variables were incorporated in multivariable models; however, these variables explained only a small fraction of variance in QOL (19–38%)<sup>27, 28</sup>. In the current analyses, we expanded the covariates to include ethnicity, socioeconomic factors and Charlson comorbidity, which helped to explain greater variability in the QOL domains (up to ~50%). We also used the PROMIS 29, which provided greater specificity in terms of decrements in specific symptom domains over and above more generalized measures of health-related QOL like physical and mental health component scores. Indeed, an important finding facilitated by discrete subdomain assessment from the PROMIS 29, is that CP leads to impairments in sleep, fatigue, and social role participation. This increased precision in symptom assessment, along with the broad validation and proliferation of PROMIS measures in studies of diverse medical conditions makes valid comparisons of symptom profiles within CP and between CP and other medical populations possible. Other strengths of our study include a large, multicenter, well-phenotyped cohort, inclusion of controls, and the use of robust statistical measures and methodology.

Our study also has limitations. Data presented are a cross-sectional assessment at the time of enrollment and not an assessment of changes in physical, mental, and social health over the disease course. Moreover, our measurement of pain is limited to severity and temporality; future studies may consider assessing perceptual qualities (e.g., sensory, neuropathic features), bodily locations and pain extent as well as assessing pain over longer measurement periods. We did not conduct diagnostic assessments of anxiety, depression or other psychological diagnoses, and rather relied on symptom measures from the PROMIS 29. However, prior studies have demonstrated criterion validity for PROMIS anxiety and depression symptom scores with clinical diagnoses of anxiety and depression.<sup>29</sup> Our use of well accepted clinical thresholds for these symptom scores likely minimizes the risk of misclassifying participants with these comorbidities. Finally, our study participants may not represent all CP patients and controls due to voluntary and non-population-based sampling used in the study.

Although causality cannot be inferred by our study, given the high rate of psychological comorbidities observed and their relationship to chronic disabling pain, it is evident that psychosocial screening and treatment are needed in the clinical management of CP. In particular, identification of anxiety, depression, sleep disturbance, and the presence of severe and constant pain may be key factors to address to improve patients' QOL. Validated screening tools, e.g. PHQ-9 can help identify clinically meaningful anxiety and depressive symptoms that warrant referral for further evaluation and treatment. Currently, there are available psychosocial interventions for management of pain and treatment of poor psychosocial functioning used in other chronic health conditions that may adapted

for use in CP. For example, cognitive behavioral therapy for chronic pain implemented in other conditions has produced positive benefits in reducing pain and disability<sup>24</sup>. There is recent preliminary evidence that internet-delivered cognitive behavioral therapy is feasible, acceptable, and reduces pain and disability in patients with definite and suspected CP<sup>30</sup>. Future research in larger-scale definitive trials is needed to evaluate whether these treatments can be applied effectively in CP to improve pain and QOL. Finally, longitudinal data are needed to understand the trajectories of pain, physical, mental, and social health over time and effects of pancreatic endotherapy and surgery.

In conclusion, this large multicenter study found a substantial impact of CP on physical, mental and social health. Among patients with CP, severe or constant pain are the major drivers for the decrements in health status. CP patients, especially those with severe or constant pain, had a high burden of clinically significant psychological and behavioral comorbidities including anxiety, depression, sleep disturbance, and low physical function. These findings highlight the need for systematic evaluation and management of psychologic comorbidities and sleep disturbance in addition to disease-specific treatments in patients with CP.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgement:

The authors thank the clinical research coordinators, laboratory staff and research personnel at the clinical centers, and staff at the Coordinating and Data Monitoring Center for their contributions to the PROCEED study. The authors are grateful to their patients for their willingness to participate in the PROCEED study.

## Funding:

Research reported in this publication was supported by the National Cancer Institute (NCI) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under award numbers: U01DK108288 (MT, SV), U01DK108300 (WGP), U01DK108306 (DY), U01DK108314 (SJP), U01DK108320 (CEF), U01DK108323 (ELF), U01DK108326 (WEF), U01DK108327 (PAH, DLC), U01DK108322 (SKV), and U01DK108328 (LL, MC, YY). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## REFERENCES.

1. Vipperla K, Kanakis A, Slivka A, et al. Natural course of pain in chronic pancreatitis is independent of disease duration. *Pancreatol* 2021;21:649–657. [PubMed: 33674197]
2. Kempeneers MA, Issa Y, Verdonk RC, et al. Pain patterns in chronic pancreatitis: a nationwide longitudinal cohort study. *Gut* 2021;70:1724–1733. [PubMed: 33158979]
3. Olesen SS, Nojgaard C, Novovic S, et al. Pain and aetiological risk factors determine quality of life in patients with chronic pancreatitis, but a brick in the puzzle is missing. *Pancreatol* 2020;20:1347–1353. [PubMed: 32948428]
4. Chasens ER, Luyster FS. Effect of Sleep Disturbances on Quality of Life, Diabetes Self-Care Behavior, and Patient-Reported Outcomes. *Diabetes Spectr* 2016;29:20–3. [PubMed: 26912961]
5. Koffel E, Kats AM, Kroenke K, et al. Sleep Disturbance Predicts Less Improvement in Pain Outcomes: Secondary Analysis of the SPACE Randomized Clinical Trial. *Pain Med* 2020;21:1162–1167. [PubMed: 31529104]

6. Phillips AE, Faghieh M, Drewes AM, et al. Psychiatric Comorbidity in Patients With Chronic Pancreatitis Associates With Pain and Reduced Quality of Life. *Am J Gastroenterol* 2020;115:2077–2085. [PubMed: 32740078]
7. Gerrits MM, Vogelzangs N, van Oppen P, et al. Impact of pain on the course of depressive and anxiety disorders. *Pain* 2012;153:429–36. [PubMed: 22154919]
8. Burgess HJ, Burns JW, Buvanendran A, et al. Associations Between Sleep Disturbance and Chronic Pain Intensity and Function: A Test of Direct and Indirect Pathways. *Clin J Pain* 2019;35:569–576. [PubMed: 30913041]
9. Amtmann D, Askew RL, Kim J, et al. Pain affects depression through anxiety, fatigue, and sleep in multiple sclerosis. *Rehabil Psychol* 2015;60:81–90. [PubMed: 25602361]
10. Uc A, Andersen DK, Apkarian AV, et al. Pancreatic Pain-Knowledge Gaps and Research Opportunities in Children and Adults: Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop. *Pancreas* 2021;50:906–915. [PubMed: 34643606]
11. Yadav D, Park WG, Fogel EL, et al. PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies: Rationale and Study Design for PROCEED From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. *Pancreas* 2018;47:1229–1238. [PubMed: 30325862]
12. Tirkes T, Shah ZK, Takahashi N, et al. Reporting Standards for Chronic Pancreatitis by Using CT, MRI, and MR Cholangiopancreatography: The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. *Radiology* 2019;290:207–215. [PubMed: 30325281]
13. Tirkes T, Shah ZK, Takahashi N, et al. Inter-observer variability of radiologists for Cambridge classification of chronic pancreatitis using CT and MRCP: results from a large multi-center study. *Abdom Radiol (NY)* 2020;45:1481–1487. [PubMed: 32285180]
14. 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]
15. National Institutes of Health. Office of Strategic Coordination - The Common Fund. Patient Reported Outcomes Measurement Information System. Available at: <https://commonfund.nih.gov/promis/index>. Accessed August 23, 2021.
16. Cook KF, Jensen SE, Schalet BD, et al. PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions. *J Clin Epidemiol* 2016;73:89–102. [PubMed: 26952842]
17. Health Measures. Transforming how health is measured. <https://www.healthmeasures.net/promis-scoring-manuals>. Accessed June 10, 2021.
18. Health Measures. Transforming how health is measured. PROMIS Score cut points. Available at: <https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/promis-score-cut-points>. Accessed 22 Aug 2021.
19. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology* 2007;18:800–4. [PubMed: 18049194]
20. Yost KJ, Eton DT, Garcia SF, et al. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System–Cancer scales in advanced-stage cancer patients. *J Clin Epidemiol* 2011;64:507–16. [PubMed: 21447427]
21. Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Med* 2011;12:996–1004. [PubMed: 21752179]
22. Dominguez-Munoz JE, Drewes AM, Lindkvist B, et al. Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis. *Pancreatol* 2018;18:847–854. [PubMed: 30344091]
23. Gardner TB, Adler DG, Forsmark CE, et al. ACG Clinical Guideline: Chronic Pancreatitis. *Am J Gastroenterol* 2020;115:322–339. [PubMed: 32022720]
24. Williams ACC, Fisher E, Hearn L, et al. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* 2020;8:CD007407. [PubMed: 32794606]

25. Tang NK, Lereya ST, Boulton H, et al. Nonpharmacological Treatments of Insomnia for Long-Term Painful Conditions: A Systematic Review and Meta-analysis of Patient-Reported Outcomes in Randomized Controlled Trials. *Sleep* 2015;38:1751–64. [PubMed: 25902806]
26. Vitiello MV, McCurry SM, Shortreed SM, et al. Short-term improvement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. *Pain* 2014;155:1547–1554. [PubMed: 24793909]
27. Amann ST, Yadav D, Barmada MM, et al. Physical and mental quality of life in chronic pancreatitis: a case-control study from the North American Pancreatitis Study 2 cohort. *Pancreas* 2013;42:293–300. [PubMed: 23357924]
28. 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]
29. Bernstein CN, Zhang L, Lix LM, et al. The Validity and Reliability of Screening Measures for Depression and Anxiety Disorders in Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2018;24:1867–1875. [PubMed: 29668911]
30. Palermo TM, Law EF, Topazian MD, et al. Internet Cognitive-Behavioral Therapy for Painful Chronic Pancreatitis: A Pilot Feasibility Randomized Controlled Trial. *Clin Transl Gastroenterol* 2021;12:e00373. [PubMed: 34140460]

**WHAT YOU NEED TO KNOW.****BACKGROUND.**

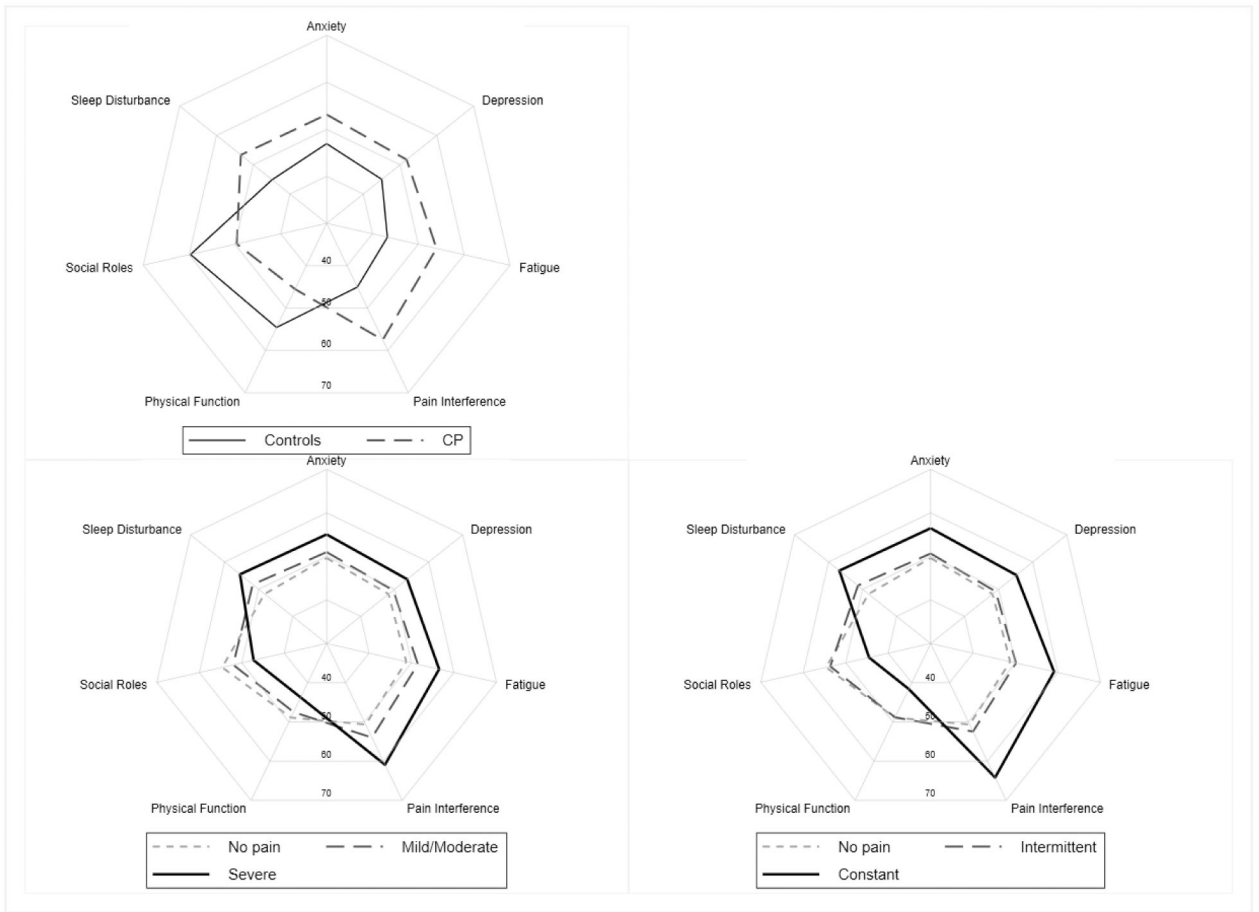
- Abdominal pain is a major driver for poor quality of life in chronic pancreatitis. Outcomes for treatments for abdominal pain in patients with chronic pancreatitis are suboptimal.

**FINDINGS.**

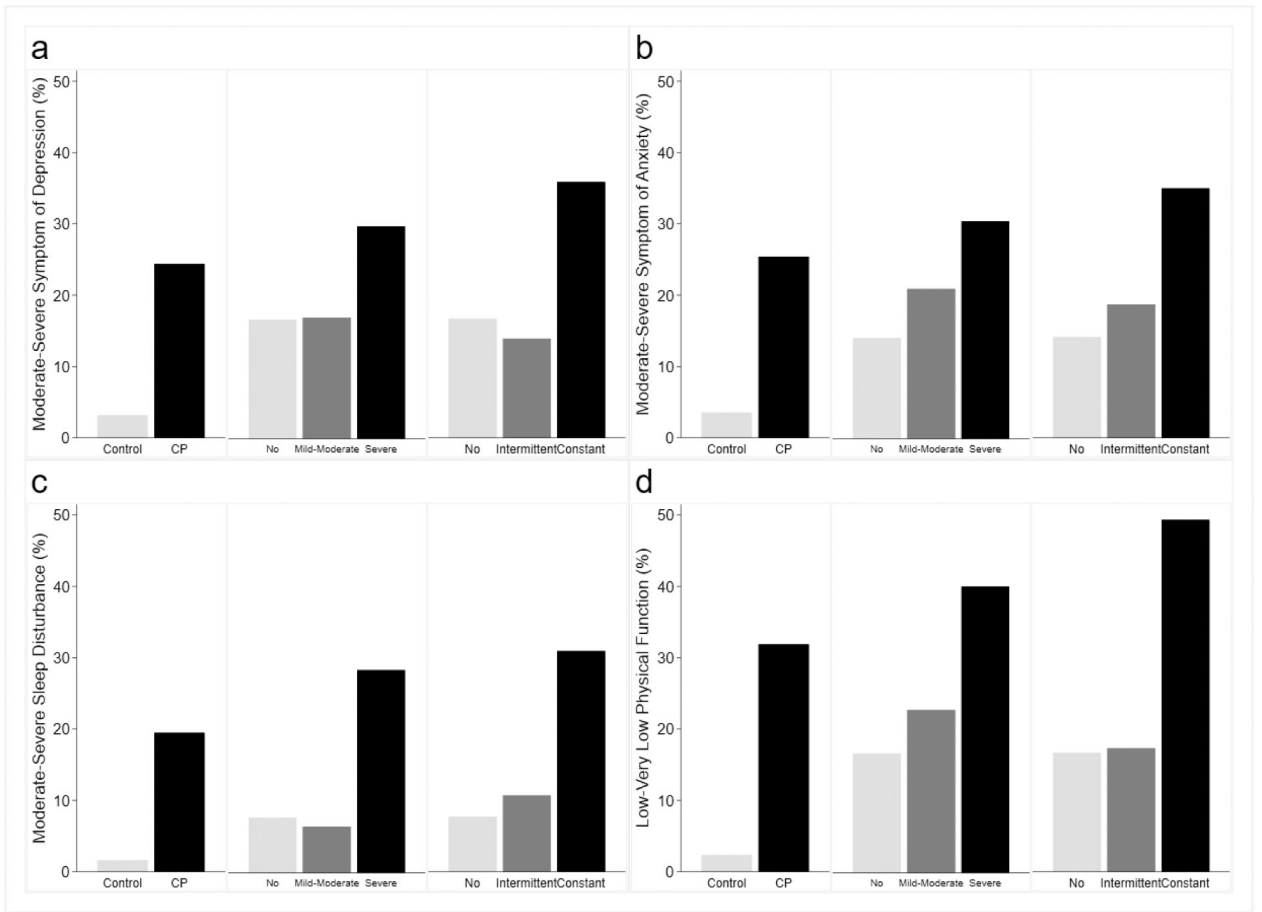
- Chronic pancreatitis participants with severe or constant pain (vs. no pain) had significant decrements in physical, mental, and social health; and had greater prevalence of moderate-severe symptoms of depression, anxiety, sleep disturbance and low physical function.

**IMPLICATIONS FOR PATIENT CARE.**

- The evaluation and treatment of psychological and behavioral comorbidities may improve outcomes for pain management of patients with chronic pancreatitis.



**Figure 1.** Radar chart showing PROMIS 29 symptom profile\* for comparisons between participants with CP and controls (panel A), CP categorized by pain severity (panel B), and CP categorized by pain temporality (panel C)\*  
 The center of the radar plot represents a score of 30 on all seven domains of the PROMIS-29, and the outer edges of the plot represent a score of 70. Separate lines represent distinct subgroups. The further a line is from the center, the higher the mean score is on that domain. \*Comparisons for each PROMIS domain (chronic pancreatitis vs. controls; pain categories in chronic pancreatitis [severe vs. no pain, and constant vs. no pain]) were significant ( $p < 0.001$ )



**Figure 2.** Prevalence of moderate-severe symptoms of depression (panel A), anxiety (panel B), sleep disturbance (panel C), and low physical function (panel D) in participants with chronic pancreatitis

**Table 1.**

Characteristics of controls and participants with CP

| Characteristic  | Controls (n=254) | Chronic Pancreatitis (n=488) | p-value |
|---|------------------|------------------------------|---------|
| <b>Age</b> (in years) – mean (SD)   | 49.1 (14.5)      | 53.7 (12.7)                  | <0.001  |
| <b>Male – n (%)</b>   | 130 (51.2)       | 248 (50.8)                   | 0.93    |
| <b>Race - n (%)</b>   |                  |                              | 0.02    |
| Asian   | 20 (7.9%)        | 17 (3.5%)                    |         |
| Black   | 26 (10.2%)       | 33 (6.8%)                    |         |
| Other (American Indian/Alaskan Native, Native Hawaiinn, Other Pacific Islander) | 11 (4.3%)        | 22 (4.5%)                    |         |
| White   | 197 (77.6%)      | 416 (85.2%)                  |         |
| <b>Ethnicity (Hispanic) – n (%)</b>   | 21 (8.3%)        | 14 (2.9%)                    | 0.001   |
| <b>Body mass index – n (%)</b>  |                  |                              |         |
| Low/normal  | 98 (38.6%)       | 262 (53.7%)                  | <0.001  |
| Overweight  | 97 (38.2%)       | 132 (27%)                    |         |
| Obese   | 59 (23.2%)       | 94 (19.3%)                   |         |
| <b>Marital status – n (%)</b>   |                  |                              |         |
| Married/Living as Married   | 157 (62.1%)      | 277 (57%)                    | .05     |
| Single  | 60 (23.7%)       | 104 (21.4%)                  |         |
| Divorced/Separated/Widowed  | 36 (14.2%)       | 105 (21.6%)                  |         |
| Do not know/Decline to Answer/Missing   | 1                | 2                            |         |
| <b>Education – n (%)</b>  |                  |                              |         |
| High school graduate/GED or less  | 13 (5.3%)        | 173 (36%)                    | <0.001  |
| Post high school training other than college/Associate degree/ some college     | 51 (20.6%)       | 175 (36.5%)                  |         |
| Bachelor’s degree   | 94 (38.1%)       | 83 (17.3%)                   |         |
| Graduate School   | 89 (36%)         | 49 (10.2%)                   |         |
| Other/Do not know/Missing   | 7                | 8                            |         |
| <b>Employment status - n (%)</b>  |                  |                              |         |
| Employed for wages / Self-employed/Military                                     | 184 (72.4%)      | 186 (38.6%)                  | <0.001  |
| Unemployed  | 6 (2.4%)         | 148 (30.7%)                  |         |
| Homemaker   | 3 (1.2%)         | 20 (4.1%)                    |         |
| Retired   | 48 (18.9%)       | 120 (24.9%)                  |         |
| Student   | 13 (5.1%)        | 8 (1.7%)                     |         |
| Do not know/Decline to Answer/Missing   | 0                | 6                            |         |
| <b>Annual income – n (%)</b>  |                  |                              |         |
| <\$25,000   | 17 (7.3%)        | 129 (29.3%)                  | <0.001  |
| \$25,000 – <\$50,000  | 44 (18.9%)       | 98 (22.2%)                   |         |
| \$50,000 – <\$75,000  | 45 (19.3%)       | 74 (16.8%)                   |         |
| \$75,000 – <\$100,000   | 37 (15.9%)       | 39 (8.8%)                    |         |

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

| Characteristic  | Controls (n=254) | Chronic Pancreatitis (n=488) | p-value |
|---|------------------|------------------------------|---------|
| > \$100,000   | 90 (38.6%)       | 101 (22.9%)                  |         |
| Do not know/Decline to Answer/Missing   | 21               | 47                           |         |
| <b>Smoking status – n (%)</b>   |                  |                              |         |
| Never   | 187 (74.2%)      | 135 (27.8%)                  | <0.001  |
| Past  | 53 (21%)         | 155 (31.9%)                  |         |
| Current   | 12 (4.8%)        | 196 (40.3%)                  |         |
| Missing   | 2                | 2                            |         |
| <b>Drinking status – n (%)</b>  |                  |                              |         |
| Never   | 22 (8.7%)        | 65 (13.3%)                   | <0.001  |
| Past  | 36 (14.2%)       | 308 (63.1%)                  |         |
| Current   | 196 (77.2%)      | 115 (23.6%)                  |         |
| <b>Remaining variables are for participants With Chronic Pancreatitis only:</b> |                  |                              |         |
| <b>Alcohol etiology – n (%)</b>   |                  |                              |         |
| No  |                  | 280 (57.5%)                  |         |
| Yes   |                  | 208 (42.5%)                  |         |
| <b>Diabetes mellitus – n (%)</b>  |                  |                              |         |
| No  |                  | 267 (56.4%)                  |         |
| Yes   |                  | 206 (43.6%)                  |         |
| Unknown   |                  | 15                           |         |
| <b>Exocrine pancreatic dysfunction - n (%)</b>                                  |                  |                              |         |
| No  |                  | 108 (22.1%)                  |         |
| Yes   |                  | 207 (42.4%)                  |         |
| Unknown (not tested)  |                  | 173 (35.5%)                  |         |
| <b>Calcifications</b>   |                  |                              |         |
| No  |                  | 128 (26.2%)                  |         |
| Yes   |                  | 360 (73.8%)                  |         |
| <b>Endoscopic therapy</b>   |                  |                              |         |
| No  |                  | 203 (42.1%)                  |         |
| Yes   |                  | 279 (57.9%)                  |         |
| Unknown   |                  | 6                            |         |
| <b>Surgery (pancreatic)</b>   |                  |                              |         |
| No  |                  | 441 (91.3%)                  |         |
| Yes   |                  | 42 (8.7%)                    |         |
| Unknown   |                  | 5                            |         |
| <b>Charlson co-morbidity</b>  |                  |                              |         |
| 0–1   |                  | 335 (68.6%)                  |         |
| 2–3   |                  | 114 (23.4%)                  |         |
| >3  |                  | 39 (8%)                      |         |
| <b>Pain severity – n (%)</b>  |                  |                              |         |

| Characteristic                              | Controls (n=254) | Chronic Pancreatitis (n=488) | <i>p-value</i> |
|---|------------------|------------------------------|----------------|
| None  |                  | 78 (16%)                     |                |
| Mild-moderate                               |                  | 124 (25.4%)                  |                |
| Severe                                      |                  | 286 (58.6%)                  |                |
| <b>Temporal nature of pain – n (%)</b>      |                  |                              |                |
| None  |                  | 78 (16%)                     |                |
| Intermittent                                |                  | 187 (38.3%)                  |                |
| Constant                                    |                  | 223 (45.7%)                  |                |
| <b>Opioid use (current) – n (%)</b>         |                  |                              |                |
| Yes   |                  | 227 (46.7%)                  |                |
| No  |                  | 259 (53.3%)                  |                |
| Unknown                                     |                  | 2                            |                |
| <b>Neuromodulator use (current) – n (%)</b> |                  |                              |                |
| Yes   |                  | 158 (32.5%)                  |                |
| No  |                  | 328 (67.5%)                  |                |
| Unknown                                     |                  | 2                            |                |

**Table 2.**

Independent effect of CP on PROMIS measures

| Domains                     | Difference in T score (Chronic Pancreatitis vs. controls) <sup>^</sup> | 95% CI         | R-Square | p-value |
|-----------------------------|--|----------------|----------|---------|
| <b>PROMIS Global Health</b> |  |                |          |         |
| Physical Component Score    | -7.15  | (-8.65, -5.65) | .52      | <0.001  |
| Mental Component Score      | -3.13  | (-4.63, -1.62) | .39      | <0.001  |
| <b>PROMIS 29</b>            |  |                |          |         |
| Physical Function           | -4.23  | (-5.71, -2.76) | .43      | <0.001  |
| Anxiety                     | 4  | (2.26, 5.73)   | .24      | <0.001  |
| Depression                  | 2.95   | (1.31, 4.59)   | .28      | <0.001  |
| Fatigue                     | 7.01   | (5.22, 8.8)    | .38      | <0.001  |
| Sleep Disturbance           | 5.64   | (3.9, 7.37)    | .28      | <0.001  |
| Social Roles                | -5.36  | (-7, -3.71)    | .40      | <0.001  |
| Pain Interference           | 6.59   | (4.78, 8.4)    | .43      | <0.001  |

<sup>^</sup> positive or negative sign indicates whether the score is lower or higher than the comparison group

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**Table 3.** Independent effect of pain severity/temporality on PROMIS measures in participants with CP

| Domains                  |                      | Pain Severity   |                |         |          | Pain Temporality  |        |         |          |
|--------------------------|----------------------|---|----------------|---------|----------|---|--------|---------|----------|
| Domains                  | PROMIS Global Health | Difference in T-score (Reference group: No pain) <sup>^</sup> | 95% CI         | p-value | R-square | Difference in T-score (Reference group: No pain) <sup>^</sup> | 95% CI | p-value | R-square |
| Physical Component Score |                      |   |                |         | 0.40     |   |        |         | 0.47     |
| <i>Mild-moderate</i>     |                      | -1.79   | (-4.02, .43)   | .11     |          |   |        |         |          |
| <i>Severe</i>            |                      | -4.55   | (-6.63, -2.47) | <0.001  |          |   |        |         |          |
| Mental Component Score   |                      |   |                |         | 0.38     |   |        |         | 0.41     |
| <i>Mild-moderate</i>     |                      | -1.78   | (-4, .45)      | .12     |          |   |        |         |          |
| <i>Severe</i>            |                      | -2.54   | (-4.62, -.45)  | .02     |          |   |        |         |          |
| <b>PROMIS 29</b>         |                      |   |                |         |          |   |        |         |          |
| Physical Function        |                      |   |                |         | 0.35     |   |        |         | 0.39     |
| <i>Mild-moderate</i>     |                      | -1.73   | (-4.07, .62)   | .15     |          |   |        |         |          |
| <i>Severe</i>            |                      | -3.46   | (-5.65, -1.26) | .002    |          |   |        |         |          |
| Anxiety                  |                      |   |                |         | 0.23     |   |        |         | 0.25     |
| <i>Mild-moderate</i>     |                      | .55   | (-2.12, 3.22)  | .69     |          |   |        |         |          |
| <i>Severe</i>            |                      | 2.72  | (.22, 5.22)    | .03     |          |   |        |         |          |
| Depression               |                      |   |                |         | 0.26     |   |        |         | 0.28     |
| <i>Mild-moderate</i>     |                      | .7  | (-1.87, 3.27)  | .59     |          |   |        |         |          |
| <i>Severe</i>            |                      | 2.88  | (.47, 5.29)    | .02     |          |   |        |         |          |
| Fatigue                  |                      |   |                |         | 0.34     |   |        |         | 0.39     |
| <i>Mild-moderate</i>     |                      | 1.9   | (-.73, 4.53)   | .16     |          |   |        |         |          |
| <i>Severe</i>            |                      | 4.1   | (1.64, 6.56)   | .001    |          |   |        |         |          |
| Sleep Disturbance        |                      |   |                |         | 0.24     |   |        |         | 0.26     |
| <i>Mild-moderate</i>     |                      | 2.16  | (-.36, 4.68)   | .09     |          |   |        |         |          |
| <i>Severe</i>            |                      | 4.92  | (2.56, 7.28)   | <0.001  |          |   |        |         |          |
| Social Roles             |                      |   |                |         | 0.34     |   |        |         | 0.41     |

| Domains              | Pain Severity   |                |         |          | Pain Temporality  |                |         |          | R-square |
|----------------------|---|----------------|---------|----------|---|----------------|---------|----------|----------|
|                      | Difference in T-score (Reference group: No pain) <sup>^</sup> | 95% CI         | p-value | R-square | Difference in T-score (Reference group: No pain) <sup>^</sup> | 95% CI         | p-value | R-square |          |
| <i>Mild-moderate</i> | -1.51   | (-4.03, 1.02)  | .24     |          | <i>Intermittent</i>   | (-2.46, 2.03)  | .85     |          |          |
| <i>Severe</i>        | -3.92   | (-6.29, -1.56) | .001    |          | <i>Constant</i>   | (-9.14, -4.44) | <0.001  |          |          |
| Pain Interference    |   |                |         | 0.36     |   |                |         | 0.44     |          |
| <i>Mild-moderate</i> | 2.11  | (-.68, 4.9)    | .14     |          | <i>Intermittent</i>   | (-1.15, 3.72)  | .30     |          |          |
| <i>Severe</i>        | 7.03  | (4.42, 9.64)   | <0.001  |          | <i>Constant</i>   | (7.82, 12.92)  | <0.001  |          |          |

<sup>^</sup> positive or negative sign indicates whether the T-score is lower or higher than the comparison group