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Sleep disturbance improves with SARS-COV2 vaccinations in patients with Chronic Inflammatory Disease

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Abstract

Objective: Immunocompromised patients with chronic inflammatory diseases (CID) may have experienced additional psychosocial burden during the COVID-19 pandemic due to an immunocompromised status. We hypothesized that vaccination will result in improved patient-reported outcomes (PROs) longitudinally among individuals with CID undergoing SARS-CoV-2 vaccination following vaccination regardless of baseline anxiety.

Methods: Data are from a cohort of individuals with CID from two sites undergoing SARS-CoV-2 vaccination. Participants completed three study visits before and after two mRNA vaccine doses, in the initial vaccination series, where clinical data was collected. PROs were measured using the PROMIS-29 Profile and expressed as T-scores, with 2 groups stratified by high and low baseline anxiety. Mixed effects models were used to examine longitudinal changes, adjusting for age, gender, and study site.

Results: The cohort was 72% female with mean ±SD age of 48.1±15.5 years. Overall, sleep disturbance improved following both doses of SARS-CoV-2 vaccinations and anxiety decreased after the second dose. Physical function scores worsened but did not meet MID threshold. Stratifying by baseline anxiety, improvement in anxiety, fatigue, and social participation were greater for the high anxiety group. Physical function worsened slightly for both groups and sleep disturbance improved significantly in the high anxiety group.

Conclusion: Sleep disturbance decreased in a significant and meaningful way in patients with CID upon vaccination. In patients with higher baseline anxiety, social participation increased and anxiety, fatigue, and sleep disturbance decreased. Overall, results suggest that SARS-CoV-2 vaccines may improve mental health and wellbeing, particularly among those with greater anxiety.

Significance and Innovation

- Sleep disturbance upon SARS-CoV-2 vaccination has not previously been examined in the CID population, but was found to decrease significantly in this cohort.
- Those with higher baseline anxiety were more prone to beneficial effects of decreased anxiety, fatigue and sleep disturbance and increased social participation, after vaccination
- SARS-CoV-2 vaccination may have benefits beyond immunity, in improving mental health and well-being.

Introduction

As the Coronavirus Disease-2019 (COVID-19) pandemic has unfolded, people across the world have experienced a significant psychological burden with social confinement, concerns about health, potential infection, financial difficulty, and uncertainty about the future.[1] Immunosuppressed individuals with chronic inflammatory diseases (CID) may have experienced an additional burden because of their immunocompromised status, leaving them particularly at risk for worse outcomes. For example, previous studies have shown that patients with CID taking immunosuppressants, such as B cell depleting therapies or glucocorticoids, are more vulnerable to infectious diseases and have increased hospitalization and death rates from COVID-19.[2-4]

Studies show that patients with CID have lower vaccination rates or willingness to receive a SARS-CoV-2 vaccine compared to the general population. One source from Italy found that 82.3% of healthy controls accepted a vaccine compared to 54.9% of patients with rheumatic and musculoskeletal diseases (RMDs), although the latter were more likely to perceive themselves at risk of infection.[5] Notably, patients with RMDs refusing vaccination reported significantly more willingness than controls to reconsider their decision with more medical education.[5] Refusal for vaccination was largely disease-linked (28.4% fear of adverse effects related to their disease, 25.6% fear of their disease worsening, 43.5% fear of adverse regardless of their disease and 2.7% distrust in SARS-CoV-2 vaccine).[5] Similarly, a study in Pennsylvania in patients with IBD found that over a third (35.6%) expressed SARS-CoV-2 vaccine hesitancy due to concerns about safety (49.4%), efficacy (23.5%), and other non-specific concerns (34.1%).[6]

Individuals with CID may also have more mental health comorbidities, including increases in anxiety and depression during the pandemic.[7] This additional burden of anxiety during the pandemic may restrict patients with CID from social interaction and outdoor exercise and negatively impact their perceptions, which could further impact PROs factors including physical function, fatigue, anxiety, depression, sleep disturbance, social participation, pain interference and pain intensity. Therefore, we hypothesized that this group might have more pronounced changes after SARS-CoV-2 vaccination due to amelioration of these symptoms.

Vaccine administration began in spring 2021, which offered protections from severe health outcomes from COVID-19. This reduction in risk may have reduced anxiety over COVID-19, particularly for individuals with CID, who were at elevated risk of severe COVID-19 complications. The purpose of this study was to address a current gap in our understanding of how vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) impacts individuals with CID in terms of mental health and quality of life.

Patients and Methods

Data Source. Data were from a prospective cohort study of patients with CID undergoing SARS-CoV-2 vaccination, recruited from the faculty, employees, staff, and patients at two sites, Washington University School of Medicine and BJC Healthcare system (St. Louis, MO, USA) and the University of California, San Francisco (UCSF), UCSF Health, and Zuckerberg San Francisco General (ZSFG) Hospital (San Francisco, CA, USA). The cohort was developed as a longitudinal, prospective, observational study, SARS-CoV-2 Vaccine Responses in Patients with Autoimmune Disease (COVaRiPAD), to examine the quality and magnitude of immune response to the mRNA

SARS-CoV-2 vaccines. Participants were recruited from 12/10/2020 to 3/20/2021, and all participants provided written informed consent. The research protocol was approved by the University of California, San Francisco and Washington University in St. Louis Institutional Review Boards.

Participants at each site were recruited from the institutions' and the universities' specialty clinics (Rheumatology, Gastroenterology, Dermatology, and Neurology). Patients were eligible if they were 18 years of age, COVID-19 naïve (no prior infection ever), and have a healthcare documented autoimmune disease. Participants were not eligible if they had any history of allergy to vaccination, Guillan-Barre post vaccination, an acute illness within 72 hours before vaccination, history of uncontrolled HIV or cancer, any other chronic uncontrolled illnesses, history of excessive alcohol or drug use, recipient of any blood products or immunoglobulin 90 days after vaccination, or have received any other vaccine 60 days after the vaccination visit. Diagnosis of a CID was confirmed by chart review and assessed in a baseline survey along with demographic information. Once participants were consented for the study, they completed up to three study visits (baseline before vaccination (T1), after dose 1 (T2), and after dose 2 (T3)), at which time the clinical data were collected. Surveys for T2 and T3 were completed 7-10 days after each vaccine administration. Participants could opt to donate blood specimens and not complete the surveys.

Outcomes. Primary outcome measures were T-scores from each of the 7 patient-reported outcomes measured with the Patient Reported Outcomes Measurement Information System 29-item Profile (PROMIS-29 v2.1). This is a validated tool which includes 4-item scales for 7

domains (physical function, fatigue, anxiety, depression, sleep disturbance, social participation, pain interference) and a 1-item pain severity question. The PROMIS-29 was administered at each time point, and scores were generated from raw data via Health Measures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice). Higher PROMIS scores reflect "more" of the construct being measured. Therefore, increases in physical function and social participation scores reflect improvements over time; decreases in fatigue, anxiety, depression, sleep disturbance, and pain interferences reflect improvements. Minimally important differences (MID) were based on published values for systemic lupus erythematosus,[8] acknowledging that these values may be different for other CIDs.

Additional variables. Other covariates including CID diagnoses, medications, race/ethnicity, gender, and age were collected through baseline surveys at the first visit (T1). This information was confirmed by chart review. Race and ethnic background was determined by survey from a fixed set of choices and ability to select from multiple categories: 1) White (from Europe, Middle East, or North Africa) 2) Black or African-American (any of the black racial groups of Africa) 3) Asian (any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent) 4) Native American Indian or Alaska Native 5) Native Hawaiian or Other Pacific Islander (from Hawaii, Guam, Samoa or other Pacific Islands) 6) Latino or of Hispanic origin or descent 7) Mix (If mixed race, check race of each parent) 8) Unknown. Since most of our patients were of White non-Hispanic ethnicity, we utilized a dichotomous variable to reflect non-European ancestry. Education and disease duration were available in a subset of UCSF

patients (n=98); education was considered as a dichotomous variable (college degree or less, n=46; post-graduate n=52).

Statistical analysis. Descriptive statistics were summarized with means and frequencies for the entire cohort. Mixed effects models were used to examine changes in the PROMIS scores compared to baseline after both vaccination doses, with repeated measures of each subject as a random effect and adjusting for age, gender and study site. Mixed models are used to account for correlation in repeated measures from individual patients; they also have the advantage of accommodating missing data so all observations available can be included in the regression models. Statistical significance was determined using a Bonferroni-corrected threshold of p <=0.003 to account for testing 7 outcomes at two time points. Vaccine type (Pfizer or Moderna) and non-European ethnicity were not significant covariates in any model (p>0.3) and were therefore not included in the final analyses. Education and disease duration, analyzed in a subset of patients, were not associated with differences between T2 and T1 or T3 and T1 for any score (p>0.1). All analyses were conducted using Stata® version 13.

Additional analyses examined trends among participants with high vs. low baseline PROMIS anxiety scores**.** High baseline anxiety was defined as a score ≥55 (one-half standard deviation above the population mean, a proxy for a clinically important change).[9]

Results

T1, T2, and T3 questionnaires were completed by 171 (81.4%), 202 (96.2%) and 197 (93.8%) participants at WUSTL, and 43 (43%), 64 (64%) and 87 (87%) participants at UCSF, respectively.

The cohort was 72% female with a mean age of 48.1±15.5 years (Table 1). Three quarters of the participants received the BNT162b2 Pfizer vaccine. The most frequent diagnoses were inflammatory bowel disease (32.3%), rheumatoid arthritis (25.5%), and spondyloarthritis (19.4%). The most common medication exposures included hydroxychloroquine (18.7%), methotrexate (18.1%) and prednisone (12.3%).

PROMIS scores at each time point are shown in Table 2. In the overall cohort, sleep disturbance significantly improved after both doses of SARS-CoV-2 vaccinations (T3 vs T1 T-score difference -2.5, 95%CI -3.4, -1.6, p 2.4E-08) (Table 3). Anxiety improved after the second vaccine dose. Physical function worsened at T3, although this did not meet the MID threshold (-1.0, 95% CI -1.6, -0.4, p 0.00082).[10] There were no significant changes in the other PROMIS scores using a Bonferroni correction threshold of 0.003.

In the analysis stratified by levels of baseline anxiety, improvement in anxiety at T3 was greater for the group with higher baseline anxiety (-5.4, 95% CI -7.2, -3.6 [T3 T1] p 4.2E-09 vs. lower baseline anxiety (-0.3, 95% CI -1.3, 0.7 [T3 T1] p 0.56) (Table 4). Improvements in fatigue (-2.1, 95% CI -3.6, -0.5, p 0.008) and social participation (2.3, 95% CI 0.5, 4.2, p 0.013) were also noted for the high-anxiety group. Similar to the overall cohort, physical function worsened slightly for both groups (-0.9, 95% CI -1.6, -0.2 [T3 T1] p 0.014) and sleep disturbance improved significantly (-2.5, 95% CI -3.4, -1.6 [T3 T1] p 2E-08) (Table 5).

Due to differences in responses rates at study sites, and to control for differences in the two groups, we performed sensitivity analyses to assess for any bias. Study site was included in all models; however, it was only significant for a few outcomes. There was higher anxiety (coefficient=3.0, p=0.001) and depression (coefficient=1.5, p=0.03) overall in the UCSF patients;

within the low anxiety group, UCSF patients had worse sleep (coefficient=-3.6, p=0.02). The sensitivity analysis excluding patients who did not complete the Time 1 questionnaire (600 observations from 214 patients, average 2.8 observations/patient), showed very similar results (Supplemental Table 2). In particular, improvements in sleep disturbance were still highly significant for both Time 2 (coefficient=-2.1, p=1.9e-5) and Time 3 (coefficient=-2.4, p=2.1e-7). We also investigated effect modification of sleep disturbance score differences via meta-analysis by site (Supplemental Figure 1). While we have low power for stratified analysis, particularly for the UCSF cohort, we do see evidence of heterogeneity; however, sleep disturbance scores improve in both cohorts. The larger improvement in the WashU cohort may be explained at least in part by higher (worse) initial sleep disturbance scores.

Discussion:

In this study, we found that well-being of individuals with CID improved following SARS-CoV2 vaccination. This included improvements in anxiety, fatigue, sleep disturbances, and social participation, especially in those patients with higher baseline anxiety. This is especially impactful as many immunocompromised patients had higher anxiety during the pandemic.[11,12] However, as the PROMIS-29 scores illustrated improved well-being,[13] this study suggests that the vaccine may play a role greater than protection from illness by improving mental health. Particularly, the clear improvement in sleep disturbance upon vaccination is important for myriad reasons but has not previously been tracked or reported in this population. It is a critical area of research as sleep impacts immune function, affects the stress-sleep link, can prevent disruptions of social relationships, improves quality of life, and helps with coping.[14]

Studies have found that after the beginning of the COVID-19 pandemic, the incidence of sleep disturbances globally increased dramatically, due to factors relating to circadian rhythm, stress-sleep link, disrupted physical and work routines. Sleep disturbances can also be linked to depression and anxiety.[1,15-30] One study on immunocompromised adolescents with CID found a great increase in sleep disturbances in the COVID-19 pandemic in both control and CID groups, but significantly lower sleep latency in the CID group.[31] Another study found higher odds of insufficient sleep and anxiety in those with immunocompromised household members.[32] These sleep disturbances were also found to be strongly associated with impacted mental health during the COVID-19 pandemic.[33] Similarly in our cohort, we found that approximately one quarter had deficits in anxiety and sleep disturbance (defined as 0.5 SD worse than the population mean) at baseline (Supplemental Table 1).

One explanation for these increased sleep disturbances is the drastic change to people's circadian rhythm due to entrainment factors–the external cues from the environment that function as timekeepers synchronizing our biological clock to the environment.[34-35] COVID-19 increased stress, screen exposure, decreased sun exposure, and altered daily routines in many ways. With the closure of schools and activities, there was significant change in daily routines from not arising at a certain time, not showing up physically at work, as well as a loss of fixed times for eating, exercising, and engaging in social/leisure activities. Therefore, these entrainment factors normally aligning the sleep-wake cycle with the day (light) and night (dark) cycles were disrupted.[35-36] Circadian rhythm disruption can disrupt the pharmacokinetics and efficacy of therapeutic agents and vaccines, which can decrease the effectivity of the SARS-CoV-2 vaccine or COVID-19 therapy if not timed aptly or if sleep health is not considered.[37-38]

Additionally, COVID-19 related stresses may be higher in those immunocompromised, and COVID-19 related stress has been found to increase nightmares.[39]

This disruption may be particularly harmful during a pandemic as sleep, in quantity and quality, is known to be critical for immune function, physical and mental health to prevent and cope with viral illnesses and cancers.[40] Many studies have shown shift workers' vulnerabilities to cancers and COVID-19 due to disrupted circadian rhythms.[41-42] Poor sleep health not only creates vulnerability to disease, but also causes diminished antibody responses to vaccines.[43] Decreased sleep duration during the COVID-19 pandemic was found to be associated with a twofold increase in obesity, which can lead to other health problems such as diabetes.[44] Individuals with diabetes were also found to be at increased risk for poor COVID prognoses perhaps partially due to disruptions in sleep-wake cycles that impair melatonin production, immune system response, and glucose metabolism.[45] Sleep also plays a critical role in emotion regulation, and disturbances may negatively impact emotional function.[14,40] The sleep-stress link explains how anxiety and disrupted mental health can further diminish sleep quality, which in turn negatively impact mental health and enters into a negative spiral overall reducing quality of life.[1] A review summarizes that studies show that stress-related sleep problems are common, and can lead to chronic insomnia; those with better sleep quality reported fewer anxiety and PTSD symptoms during the COVID-19 outbreak.[14] For those with preexisting CID, these immune, physical and mental health complications of sleep disturbances during the COVID-19 pandemic may exacerbate the deterioration of their well-being. The findings from this study may therefore inform public health campaigns to increase vaccination rates by portraying improvements in sleep and anxiety, which have evidently been impacted globally

since the COVID pandemic and have many multifactorial negative health impacts. The clinical implications of associated health improvements from PROs may help patients from all health backgrounds, not just CID, to be encouraged to receive vaccines.

The impact of sleep disturbances is especially burdensome in patients with CID who are already vulnerable to infectious disease and worse COVID-19 outcomes due to their immunosuppressed status and lower response to vaccine. Studies have shown reduced COVID-19 antibody production in some patients with CID.[4,46] In this study, we found that sleep disturbance and anxiety decrease in a significant and meaningful way in patients with CID after the completion of the SARS-CoV-2 vaccine series. These findings of improved sleep among individuals with decreases in anxiety may represent an association between sleep and anxiety that studies such as Nami 2020 and Tsang 2021 have also reported in context of the pandemic.[28,40] In patients with higher anxiety at baseline, not only did anxiety, fatigue and sleep disturbances decrease, but there was also an increase in social participation. The decrease in sleep disturbances may also be explained by the reintroduction of entrainment factors, as vaccinated individuals were able to resume more in-person activities, which was reflected in the improvements in Social Participation scores. The fact that these changes occurred after the second dose may be explained as this higher anxiety group needed the assurance of completing both vaccine doses for greater sense of security and safety. Individual perceptions of COVID risk and therefore these improvements in PROs scores upon vaccination may also be influenced by community-level uptake of vaccines and communal adherence to precautionary measures such as masking; perhaps those from communities with lower vaccination rates and mask-wearing may have greater anxiety surrounding COVID infection and greater improvements. The

decreases in anxiety and sleep disturbances are meaningful in illustrating the positive impact of the COVID-19 vaccine on quality of life, and likely translates to the general population as well.

Physical function significantly decreased at the same time that pain intensity increased, depicting that the SARS-CoV-2 vaccines may affect physical health shortly after dose administration. Notably, the pain intensity is significantly higher after the second dose, which may be due to the immune response to the dose from memory B cells and preexisting antibodies. The improved anxiety and sleep health despite these negative physical impacts suggests that patients' relief upon vaccination outweighed any physical side effects. It is also possible that physical function did not improve along with anxiety and sleep as it may take longer than the study observation period to observe physical function improvement.

The study is limited as other reasons for sleep disturbances and anxiety were unaccounted for, such as personal issues patients faced. Active diarrhea or joint pain in IBD, restless leg syndrome linked to iron deficiency anemia or effects of corticosteroids can all impact sleep in this population. Whether or not patients were working in person and had a routine supporting a circadian rhythm, was also not accounted for. However, as there was still an overall significant effect, we believe that individual differences were not on a scale large enough to impact the overall population's experience. Although we were limited with missing data that can bias results, we used mixed models to address this while recognizing it may not fully account for patients who did not complete all timepoints. A sensitivity analysis on complete baseline data (Supplemental Table 1) did not change the results and so we do not expect that missing data impacts our overall findings. Vaccine hesitancy due to safety or data privacy concerns was also not accounted for and could have limited generalizability of results.

Lack of gender and racial diversity in the study sample, as well as study performance at 2 sites with community level-factors that could impact anxiety regarding COVID infection risk, may further limit generalizability. Additional limitations include regression to the mean, selection bias and non-randomized sample selection, as well as inability to determine whether the improvements in sleep disturbances and anxiety lasted beyond the study observation period. Future studies may benefit from observing long term patient reported outcomes. Whether their PROMIS-29 scores are associated with antibody response is another area of future study. Upon the rollout of SARS-CoV-2 booster vaccinations, it would also be of interest to study how PROs have changed over a longer period of time, and as rules regarding community precautions such as mask-wearing have similarly changed.

In conclusion, patients with CID receiving mRNA-based SARS-CoV2 vaccines experienced improvements in mental health and wellbeing, particularly those with greater anxiety prior to vaccination. Vaccination against COVID-19 may be one way for patients with CID to improve their sleep health during the COVID pandemic which can have a profound impact on many other aspects of well-being, including their underlying CID-specific disease activity and overall quality of life.

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Table 1: Demographic and Clinical Characteristics of Participants at baseline (n = 310)

	Mean ± standard deviation or N (%)
Age, years	48.1 ± 15.5
Female subjects	222 (71.6)
White non-Hispanic race	252 (81.3)
Site	
UCSF	100 (32.3)
Washington University	210 (67.7)
Vaccine received	
Pfizer	231 (74.5)
Moderna	79 (25.5)
Immunologic diagnosis	
Inflammatory bowel disease	100 (32.3)
Rheumatoid arthritis	72 (23.2)
Spondyloarthritis	60 (19.4)
Systemic lupus erythematosus	35 (11.3)
Other connective tissue disease	24 (7.7)
Multiple sclerosis / NMO	22 (7.1)
Uveitis	14 (4.5)
Vasculitis	7 (2.3)
Autoinflammatory syndrome	3 (1.0)
IgG4-related disease	2 (0.7)
Other	6 (1.9)
Medications	
Prednisone	38 (12.3)
Disease Modifying Antirheumatic Drug	
Methotrexate	56 (18.1)
Hydroxychloroquine	58 (18.7)
Mycophenolate mofetil	16 (5.2)
Azathioprine	19 (6.1)
Leflunomide	11 (3.6)
Sulfasalazine	19 (6.1)
Janus kinase inhibitors	17 (5.5)
Biologic therapies	
Tumor necrosis factor inhibitors	95 (30.6)
B-cell depleting therapies	29 (9.4)
Belimumab	4 (1.3)
Vedolizumab	25 (8.1)
Interleukin 12/23 or 23 inhibitors	20 (6.5)

Interleukin 17 inhibitors	2 (0.65)
Nonsteroidal anti-inflammatory drugs	58 (18.7)

Table 2. PROMIS scores at each time point

	Time 1 (before vaccination, n = 214)	Time 2 (after dose 1, n = 266)	Time 3 (after dose 2, n = 284)
Physical Function	51.1 ± 7.8	50.7 ± 8.4	50.2 ± 8.8
Fatigue	49 ± 10.2	49.7 ± 9.9	50.2 ± 10.3
Anxiety	48.1 ± 8.5	47.8 ± 7.9	47.1 ± 7.9
Depression	45.3 ± 6.3	44.8 ± 6.3	44.7 ± 6.4
Sleep Disturbance	50.4 ± 7.6	49.2 ± 8.3	48.4 ± 8.8
Social Participation	55.5 ± 8.8	55.2 ± 9.1	55.3 ± 9.1
Pain Interference	50.3 ± 8.6	49.7 ± 9.3	50.4 ± 9.1
Pain Intensity	2.3 ± 2.2	2.1 ± 2.2	2.4 ± 2.4

Table 3. Results of mixed models analysis comparing baseline PROMIS Scores with follow-up scores

	Time 2 vs. 1			Time 3 vs. 1		
	Coeff	p-value	95%CI	Coeff	p-value	95%CI
Physical Function	-0.9	0.004	-1.5, -0.3	-1.0	0.0008	-1.6, -0.4
Fatigue	0.4	0.39	-0.6, 1.4	1.0	0.05	-0.01, 1.9
Anxiety	-0.5	0.24	-1.4, 0.3	-1.5	0.0005	-2.3, -0.7
Depression	-0.2	0.59	-0.8, 0.5	-0.5	0.2	-1.1, 0.2
Sleep Disturbance	-1.7	0.0003	-2.5, -0.8	-2.5	2E-08	-3.4, -1.6
Social Participation	-0.3	0.51	-1.2, 0.6	-0.02	0.95	-0.9, 0.8
Pain Interference	-0.1	0.85	-1.0, 0.8	0.5	0.3	-0.4, 1.4
Pain Intensity	-0.1	0.57	-0.3, 0.2	0.3	0.01	0.1, 0.5

Sample Size: 764 observations from 310 subjects (average 2.5 observations/subject)
Coeff = Beta coefficient from regression analysis

Table 4. PROMIS scores at each time point stratified by baseline PROMIS Anxiety score

	Time 1 (before vaccination)		Time 2 (after dose 1)		Time 3 (after dose 2)	
	Low anxiety (n = 163)	High anxiety (n = 51)	Low anxiety (n = 144)	High anxiety (n = 43)	Low anxiety (n = 151)	High anxiety (n = 48)
Physical Function	51.9 ± 7.0	48.4 ± 9.7	51.2 ± 7.8	46.0 ± 9.6	51.1 ± 7.7	47.1 ± 10.0
Fatigue	46.9 ± 9.6	55.5 ± 9.2	47.6 ± 9.6	55.1 ± 9.6	48.9 ± 10.1	53.4 ± 9.6
Anxiety	44.3 ± 5.1	60.4 ± 5.0	44.6 ± 6.1	56.6 ± 6.4	43.9 ± 6.1	55.0 ± 6.6
Depression	43.4 ± 4.6	51.2 ± 7.4	43.5 ± 5.0	50.5 ± 7.6	42.8 ± 4.7	50.2 ± 7.7
Sleep Disturbance	49.8 ± 7.8	52.4 ± 6.6	47.9 ± 8.3	50.8 ± 7.3	47.3 ± 9.1	50.4 ± 7.3
Social Participation	57.2 ± 8.1	49.9 ± 8.9	56.0 ± 8.6	51.8 ± 10.6	56.8 ± 8.4	52.4 ± 9.7
Pain Interference	49.0 ± 8.2	54.4 ± 8.6	49.2 ± 8.8	53.3 ± 10.7	49.9 ± 8.8	53.7 ± 8.8
Pain Intensity	2.0 ± 2.0	3.1 ± 2.3	1.9 ± 2.1	3.2 ± 2.6	2.1 ± 2.1	3.1 ± 2.6

Table 5. Changes in PROMIS scores stratified by baseline PROMIS Anxiety score (<55 vs. ≥55)

Low baseline anxiety						
	Time 2 vs. 1			Time 3 vs. 1		
	Coeff	p-value	95%CI	Coeff	p-value	95%CI
Physical Function	-0.6	0.1	-1.3, 0.1	-0.9	0.014	-1.6, -0.2
Fatigue	0.4	0.59	-0.9, 1.6	2.0	0.001	0.8, 3.2
Anxiety	0.3	0.52	-0.7, 1.3	-0.3	0.56	-1.3, 0.7
Depression	0.2	0.64	-0.6, 0.9	-0.4	0.3	-1.1, 0.3
Sleep Disturbance	-2.2	0.00019	-3.3, -1.0	-2.6	4.3E-06	-3.7, -1.5
Social Participation	-1.0	0.051	-2.1, 0.01	-0.5	0.32	-1.5, 0.5
Pain Interference	0.2	0.69	-0.9, 1.4	0.9	0.12	-0.2, 2.1
Pain Intensity	-0.1	0.52	-0.4, 0.2	0.3	0.01	0.1, 0.6
High baseline anxiety						
	Time 2 vs. 1			Time 3 vs. 1		
	Coeff	p-value	95%CI	Coeff	p-value	95%CI
Physical Function	-1.8	0.004	-3.0, -0.6	-1.3	0.04	-2.4, -0.1
Fatigue	-0.4	0.6	-2.1, 1.2	-2.1	0.01	-3.6, -0.5
Anxiety	-3.7	0.0001	-5.6, -1.8	-5.4	4E-09	-7.2, -3.6
Depression	-0.7	0.4	-2.4, 1.0	-1.2	0.2	-2.8, 0.4
Sleep Disturbance	-1.8	0.03	-3.4, -0.2	-2.0	0.01	-3.5, -0.4
Social Participation	1.9	0.046	0.03, 3.9	2.3	0.01	0.5, 4.2
Pain Interference	-1.3	0.2	-3.1, 0.5	-0.9	0.3	-2.6, 0.8
Pain Intensity	0.02	0.9	-0.4, 0.5	0.03	0.9	-0.4, 0.5

Sample Sizes:
High Baseline Anxiety: 142 observations from 51 subjects (average 2.8 observations/subject)
Low Baseline Anxiety: 458 observations from 163 subjects (average 2.8 observations/subject)
Adjusted for age, gender and study site
Coeff = Beta coefficient from regression analysis