WEIGHTBEARING AND ACTIVITY RESTRICTION TREATMENTS AND QUALITY OF LIFE IN PATIENTS WITH PERTHES DISEASE

by

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ABSTRACT
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BACKGROUND: Weightbearing and activity restrictions are commonly prescribed during the active stages of Perthes disease. These restrictions, ranging from cast or brace treatment with nonweightbearing to full weightbearing with activity restrictions, may have a substantial influence on the physical, mental, and social health of a child. However, their impact on the patient's quality of life is not well-described.

OBJECTIVES: After controlling for confounding variables, are restrictions on weightbearing and activity associated with physical health measures (as expressed by the Patient-Reported Outcome Measurement Information System [PROMIS] mobility, PROMIS pain interference, and PROMIS fatigue), mental health measures (PROMIS depressive symptoms and PROMIS anxiety), and social health measures (PROMIS peer relationships)?

METHODS: Between 2013 and 2020, 211 patients with Perthes disease at a single institution were assigned six PROMIS measures to assess physical, mental, and social health. Patients who met the following eligibility criteria were analyzed: age 8 to 14 years old, completion of six PROMIS measures, English-speaking, and active stage of Perthes disease (Waldenstrom

Stage I, II, or III). Weightbearing and activity restrictions were clinically recommended to patients in the initial through early reossification stages of Perthes disease when patients had increasing pain, loss of hip motion, loss of hip containment, progression of femoral head deformity, increased hip synovitis, and femoral head involvement on magnetic resonance imaging (MRI), or as a postoperative regimen. Patients were categorized into four intervention groups based on weightbearing and activity regimen. We excluded 111 patients who did not meet the inclusion criteria. The following six pediatric self-report PROMIS measures were assessed: mobility, pain interference, fatigue, depressive symptoms, anxiety, and peer relationships. Analysis of variance (ANOVA) was used to compare differences between the mean PROMIS T-scores of these weightbearing/activity regimens. Results were assessed with a significance of $p < 0.05$ and adjusted for Waldenstrom stage, gender, age of diagnosis, and history of major surgery using multivariate regression analysis.

RESULTS: After controlling for confounding variables, the mild- (β regression coefficient -15 [95% CI -19 to -10]; $p < 0.001$), moderate- (β -19 [95% CI -24 to -14]; $p < 0.001$), and severe- (β -25 [95% CI -30 to -19]; $p < 0.001$) restriction groups were associated with worse mobility T-scores compared with the no-restriction group, but no association was detected for the pain interference or fatigue measures. Weightbearing and activity restrictions were not associated with mental health measures (depressive symptoms and anxiety). Weightbearing and activity restrictions were not associated with social health measures (peer relationships). Earlier Waldenstrom stage was associated with worse pain interference (β 10 [95% CI 2 to 17]; $p = 0.01$) and peer relationships scores (β -8 [95% CI -15 to -1]; $p = 0.03$); female gender

was linked with worse depressive symptoms (β 7 [95% CI 2 to 12]; p = 0.005) and peer relationships scores (β -6 [95% CI -12 to 0]; p = 0.04); and earlier age at diagnosis was associated with worse peer relationships scores (β 1 [95% CI 0 to 2]; p = 0.03). History of major surgery had no connection to any of the six PROMIS measures.

CONCLUSION: We found that weightbearing and activity restriction treatments are associated with poorer patient-reported mobility in the active stages of Perthes disease after controlling for confounding variables, but not pain interference, fatigue, depressive symptoms, anxiety, or peer relationships. Understanding how these treatments are associated with Perthes disease patients' quality of life can aid in decision-making for providers, help set expectations for patients and their parents, and provide opportunities for better education and preparation. Because of the chronic nature of Perthes disease, future studies may focus on longitudinal trends in patient-reported outcomes to better understand the overall impact of this disease and its treatment.

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CHAPTER 1: INTRODUCTION

Perthes disease is characterized by avascular necrosis of the femoral head, which causes hip pain, limping, and decreased ROM in children. Although Perthes disease affects a wide age range of patients, varying from 2 to 14 years old, patients older than 8 years of age at the onset of the disease have a worse prognosis than younger patients, as there is less remodeling potential of the deformed femoral head. Therefore, various nonoperative and operative treatments are instituted to decrease the progression of femoral head deformity [25]. Weightbearing and activity restrictions are commonly prescribed during the initial, fragmentation, and early reossification stages of the disease when the femoral heads are susceptible to deformation and loss of containment. These restrictions range from abduction casting to nonweightbearing with crutches to full weightbearing with activity restrictions [21, 22, 31, 35, 37].

Very little is known about the association of weightbearing and activity restriction treatments on patients' quality of life. Patient-reported outcomes (PROs) have become increasingly valuable in assessing patients' health-related quality of life [1, 4, 8, 18]. Although Perthes disease treatment evaluation has traditionally been based on physical findings and radiographic outcome classifications, PRO measures may better capture patients' perceived physical function and the psychosocial consequences of treatment [15, 16, 22, 26]. Understanding the association between weightbearing/activity restrictions and the quality of life of patients with Perthes disease may help guide expectations and education for care providers, parents, and patients [30]. Few studies have evaluated PROs and quality of life in patients with Perthes disease, and most of these had a sample size of fewer than 25

patients or used PRO measurement tools that are not specifically validated for Perthes disease [27, 29, 32, 33, 40]. Most of the other quality of life measurement tools, such as EuroQoL and Pediatric Quality of Life (PedsQL™), are not widely available for use [8, 27, 29, 32, 33]. Furthermore, none of these studies specifically addressed the association between various weightbearing/activity restrictions and the quality of life of patients with Perthes disease. Thus, the questions of whether and to what degree weightbearing and activity restrictions are associated with the quality of life in patients with Perthes disease remain unanswered. Appreciating these associations could help future studies examine the relationships of these restrictions on quality of life over time. The National Institutes of Health's Patient-Reported Outcome Measurement Information System (PROMIS) is a set of publicly available patient-centered instruments, which includes measures of physical, mental, and social health [36]. In contrast to other patient-reported outcome measurement tools, PROMIS is widely available for use with pediatric normative data and is specifically validated in Perthes disease patients [30].

We theorized that more restrictions on weightbearing and activities would be associated with worse patient-reported mobility, pain interference, fatigue, anxiety, depressive symptoms, and peer relationships.

Therefore, we asked: After controlling for confounding variables, (1) are restrictions on weightbearing and activity associated with physical health measures (as expressed by the PROMIS mobility, PROMIS pain interference, and PROMIS fatigue) of patients in the active stages of Perthes disease? (2) Are these restrictions associated with poorer scores for mental health measures (PROMIS depressive symptoms and PROMIS anxiety)? (3) Are these

restrictions associated with poorer scores for social health measures (PROMIS peer relationships)?

CHAPTER 2: METHODS

Study Design and Setting

We retrospectively gathered demographic data and PROMIS scores from institutional review board-approved sources containing the information of patients who presented to a tertiary referral care center. Using a cross-sectional survey design, the description of activity restrictions and disease stage were collected from the same visit that PROMIS data collection occurred. Before 2018, patients completed PROMIS computer adaptive test (CAT) measures; starting in 2018 patients completed fixed PROMIS short-forms. Questions for both CAT and fixed short-form measures are derived from the same item bank and were automatically assigned to patients with a Perthes disease visit type.

Participants

We collected data from all 211 patients diagnosed with Perthes disease who completed PROMIS measures during a regular clinic visit between November 2013 and April 2020. Inclusion criteria for this study were: age 8 to 14 years old at the time they took the PROMIS survey, completion of six PROMIS measures, English-speaking, and active stage of Perthes disease (Waldenstrom Stage I, II, or III). Weightbearing and activity restrictions were clinically recommended to patients in the initial through early reossification stages of Perthes disease when patients had increasing pain, loss of hip motion, loss of hip containment, progression of femoral head deformity, increased hip synovitis, and femoral head involvement on MRI, or as a postoperative regimen. Patients were categorized into four intervention groups based on weightbearing and activity restriction regimen.

As recommended by the developers of PROMIS, patients had to be at least 8 years old to

complete the measures to ensure the accuracy of responses [5, 6, 19, 20, 43]. The diagnosis of Perthes disease was determined based on history and radiographic findings using AP and frog-leg lateral radiographs. The senior author (HKWK) assigned the modified Waldenstrom stage to affected hips at the time of the patient's visit [24]. Waldenstrom Stages I through III were considered the active stages of the disease, as the femoral head can further deform and many patients receive active treatments during these stages. Stage IV was considered the healed stage. For patients who were affected with Perthes disease bilaterally (n = 24), the hip in the earlier, active stage at the time of the visit was analyzed. The senior author (HKWK) reviewed AP radiographs in the mid-fragmentation stage for lateral pillar classification. Surgical history was collected based on chart review, and major surgery was defined as proximal femoral osteotomy or core decompression using a small diameter drill or K-wire.

Among the 211 patients who received the six PROMIS pediatric self-report measures, 111 patients were excluded: 47 patients were younger than 8 years of age at the time of the survey, 60 patients had hips in the healed stage, two patients were non-English-speaking, one patient had not fully completed the six measures, and one patient had autism spectrum disorder. There remained 100 English-speaking patients with hips in the active stages for analysis (Fig. 1). The median (range) age at diagnosis was 8 years old (2 to 13). The median age at the time of PROMIS administration was 9 years old (8-14). There were 85 boys and 15 girls. Eleven patients had hips in Waldenstrom Stage I, 10 were in Stage II, and 79 were in Stage III. Forty-four patients had hips classified as lateral pillar B and 47 patients as lateral pillar C. Nine patients had not reached the mid-fragmentation stage for appropriate lateral pillar classification by the time they took the PROMIS survey. Thirty-nine percent (39 of 100)

of patients had undergone a major surgery, defined as proximal femoral osteotomy or core decompression using a small diameter drill or K-wire, before PROMIS survey administration. There were 36 patients in the no-restriction group, 27 patients in the mild-restriction group, 25 patients in the moderate-restriction group, and 12 patients in the severe-restriction group. There was no difference in the median age at the time of PROMIS administration ($f\ 2 = 0.02$; $p = 0.58$), gender ($X\ 2 = 7.71$; $p = 0.05$), lateral pillar class ($X\ 2 = 3.79$; $p = 0.29$), or history of major surgery ($X\ 2 = 3.83$; $p = 0.28$) among the four weightbearing/activity restriction groups. However, there was a difference in the median age at diagnosis ($f\ 2 = 0.28$; $p < 0.001$) and Waldenstrom stage ($X\ 2 = 18.55$; $p = 0.005$) among the four weightbearing/activity restriction groups (Table 1).

As expected, our cross-sectional sample reflects known demographics about Perthes disease patients. The 85 males and 15 females were consistent with known male-to-female ratios reported in Perthes disease epidemiology studies, which is commonly 5:1 [28]. Most patients were in the reossification stage (Waldenstrom Stage III) compared with the earlier stages, which likely reflects the long duration of the reossification stage compared with the earlier stages. According to Herring et al. [17], the reossification stage is the longest stage of Perthes disease, with a mean duration of 53 months in those patients who develop a flattened femoral head compared with a mean duration of 10 months for the fragmentation stage in these patients.

Weightbearing and Activity Restriction Regimens

In general, weightbearing and activity restrictions were recommended to patients in the initial through early reossification stages of Perthes disease when patients had increasing pain,

loss of hip motion, loss of hip containment, progression of femoral head deformity, increased hip synovitis, and femoral head involvement on MRI, or as a postoperative regimen. Prescribed weightbearing and activity restrictions described in the patient chart were categorized into four regimens, with each level being distinct from the next to ensure reproducibility. During the period of this study, patients who were asymptomatic and had favorable progression of femoral head deformity were prescribed the no-restriction regimen, which consisted of patients who were allowed to bear weight as tolerated and were allowed to participate in all activities. Patients who had low femoral head involvement, were mildly symptomatic, or were recovering from previous surgery were assigned to the mild-restriction regimen, which included patients who were allowed to return to normal walking, but not sports, physical education class at school, running, or jumping. Patients who had good hip ROM but were at risk of femoral head collapse were assigned to the moderate-restriction regimen, which included patients who were nonweightbearing, toe-touch weightbearing, or partial weightbearing to the affected hip with the use of a wheelchair, a walker, and/or crutches for mobility. Patients who had a high degree of hip stiffness were designated to the severe-restriction regimen, where patients were treated with a Petrie abduction cast, a hip spica cast, or an A-frame abduction orthosis plus were nonweightbearing on the affected side [37].

PROMIS Pediatric Self-Reported Measures and Administration

Patients completed six PROMIS pediatric self-report measures on mobile electronic tablets during a regular in-person clinic visit with the treating surgeon provider. Patients receiving measures after 2018 completed automatically assigned short-form versions of

PROMIS as part of their clinic visit through Epic (Epic Systems Corp, Verona, WI, USA). The measures are automatically assigned by EPIC based on a predetermined Perthes disease visit type. Patients receiving measures prior to 2018 completed CAT measures through REDCap (Vanderbilt University, Nashville, TN, USA). CAT is a dynamic form of testing that optimizes the item bank by using the patient's previous responses to generate the next question and reduces the number of questions needed to provide an accurate T-score [2]. Conversely, each selected fixed short-form asks eight questions, except the fatigue short-form which asks 10 questions. Questions for both CAT and fixed short-form measures are derived from the same item bank [11] . PROMIS item banks were developed based on item response theory modeling where results for each PROMIS measure, regardless of administration method, are on the same scale and are directly comparable. Studies correlating short forms to item banks and short forms to CAT have found correlations exceeding 0.95 for the respective PROMIS measures in this study [3, 36, 42]. Physical health was assessed using the PROMIS Pediatric Bank v2.0 Mobility/Short-form v2.0 Mobility 8a, PROMIS Pediatric Bank v2.0 Pain Interference/Short-form v2.0 Pain Interference 8a, and PROMIS Pediatric Bank v2.0 Fatigue/Short-form v2.0 Fatigue 10a measures. Mental health was assessed using the PROMIS Pediatric Bank v2.0 Depressive Symptoms/Short-form v2.0 Depressive Symptoms 8a and PROMIS Pediatric Bank v2.0 Anxiety/Short-form v2.0 Anxiety 8a measures. Social health was assessed using the PROMIS Pediatric Bank v2.0 Peer Relationships/Short-form v2.0 Peer Relationships 8a measure. All questions are prefaced with "In the past 7 days…". Patients answered each question based on a 5-point Likert scale ranging from "never" to "almost always," except for the mobility measure response scale, which ranges from "with no

trouble" to "not able to do."

For quantitative analysis, the raw scores of each short form were summed and converted to T-scores using publicly-accessible PROMIS scoring manuals [13]. PROMIS T-scores were normalized and calibrated to a diverse pediatric population of more than 4000 healthy and nonhealthy children of varying ages, races, and ethnicities in the United States [5, 20, 34]. For each measure, a T-score of 50 represents the mean score of the age-appropriate US population with an SD of 10. A higher T-score represents more of the domain being measured or experienced. For example, a higher anxiety T-score indicates that the patient is experiencing more anxiety than the age-appropriate US population while a higher mobility score indicates that the patient is experiencing more mobility. A predetermined range of T-scores for each measure indicates whether a score is normal, mildly abnormal, moderately abnormal, or severely abnormal. For the mobility and peer relationships measures: normal is greater than 45, mildly abnormal is equal to 40 to 44.9, moderately abnormal is equal to 30 to 39.9, and severely abnormal less than 30. For the pain interference, fatigue, depressive symptoms, and anxiety domains: normal is less 50, mildly abnormal equal to 50 to 54.9, moderately abnormal equal to 55 to 64.9, and severely abnormal greater than 65 [12].

Ethical Approval

Ethical approval for this study was obtained from the institutional review board of the UT Southwestern Medical Center (STU 082012-052).

Statistical Analysis

Means and SDs were used to describe continuous variables. ANOVA with a Tukey post-hoc test was used to compare each domain of PROMIS T-scores across weightbearing

and activity restriction groups. The univariate analysis results were assessed with a cutoff of $p < 0.05$ and adjusted for covariates, including age at Perthes disease diagnosis, gender, Waldenstrom stage, and history of major surgery, using multivariate regression analysis. All statistical significance was set at $p < 0.05$. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

CHAPTER 3: RESULTS

Association of Weightbearing and Activity Restrictions and Physical Health

Patients in the mild, moderate, and severe restriction groups reported less mobility than those in the no restriction group (Fig. 2). The mean mobility T-scores of the mild- (37 ± 5; Δ = +16 [95% CI 10 to 20]; $p < 0.001$), moderate- (32 ± 8; Δ = +21 [95% CI 15 to 26]; $p < 0.001$), and severe- (27 ± 9; Δ = 26 [95% CI 19 to 33]; $p < 0.001$) restriction groups were lower than that of the no-restriction group (53 ± 9) (Table 2). There were no differences in the mean T-scores for pain interference among the weightbearing/activity restriction regimens ($f^2 = 0.09$; $p = 0.05$), and 44% of patients had T-scores within the normal range (Fig. 3). There were no differences in the mean T-scores for fatigue among the weightbearing/activity restriction regimens ($f^2 = 0.04$; $p = 0.32$), and 83% of patients had T-scores within the normal range (Fig. 4). After controlling for relevant confounding variables, the mild (β regression coefficient [β] -15 [95% CI -19 to -10]; $p < 0.001$), moderate (β -19 [95% CI -24 to -14]; $p < 0.001$), and severe (β -25 [95% CI -30 to -19]; $p < 0.001$) restriction groups were associated with worse mobility scores than the no-restriction group. Weightbearing and activity restrictions were not associated with pain interference or fatigue scores. Waldenstrom Stage I (β 10 [95% CI 2 to 17]; $p = 0.01$) and Stage II (β 10 [95% CI 2 to 17]; $p = 0.02$) were associated with worse pain interference scores compared with Waldenstrom Stage III (Table 3).

Association of Weightbearing and Activity Restrictions and Mental Health

There were no relationships between weightbearing/activity restriction and reported

depressive symptoms or anxiety (Table 2). There were no differences in the mean T-scores for depressive symptoms among the weightbearing/activity restriction regimens (f^2 = 0.03; p = 0.43), and 80% of patients had T-scores within the normal range (Fig. 5). There were no differences in the mean T-scores for anxiety among the weightbearing/activity restriction regimens (f^2 = 0.01; p = 0.76), and 70% of patients had T-scores within the normal range (Fig. 6). After controlling for relevant confounding variables, weightbearing and activity restrictions were not associated with depressive symptoms or anxiety scores. Female gender was associated with worse depressive symptoms (β 7 [95% CI 2 to 12]; p = 0.005) (Table 3).

Association of Weightbearing and Activity Restrictions and Social Health

There was no relationship between weightbearing/activity restriction and reported peer relationships (Table 2). There were no differences in the mean T-scores for peer relationships among the weightbearing/activity restriction regimens (f^2 = 0.06, p = 0.16), and 83% of patients had T-scores within the normal range (Fig. 7). After controlling for relevant confounding variables, weightbearing and activity restrictions were not associated with peer relationship scores. Waldenstrom Stage I was also associated with worse peer relationships scores compared with Waldenstrom Stage III (β -8 [95% CI -15 to -1]; p = 0.03). Female gender (β -6 [95% CI -12 to 0]; p = 0.04) and younger age at diagnosis (β 1 [95% CI 0 to 2]; p = 0.03) were associated with worse peer relationships scores (Table 3).

CHAPTER 4: DISCUSSION

Weightbearing and activity restrictions are commonly recommended for treatment of patients in the active stages of Perthes disease [22, 25]. Many questions regarding how weightbearing and activity restrictions are associated with the physical, mental, and social health of patients with Perthes disease remain unanswered. No study has previously evaluated the association between the weightbearing/activity restriction regimens and the health-related quality of life of children with Perthes disease using PROMIS measures. In a cohort of patients with Perthes disease who were able to self-report, we found that more severe weightbearing/activity restrictions were associated with worse patient-reported mobility scores. However, the pain interference, fatigue, depressive symptoms, anxiety, and peer relationships scores were not associated with the severity of weightbearing and activity restrictions. Understanding how these treatments are associated with Perthes disease patients' quality of life can aid in decision-making for providers, help set expectations for patients and their parents, provide opportunities for better education and preparation, and encourage future studies to longitudinally examine the effect of these restrictions on quality of life over time.

Limitations

This study has some limitations. First, we cannot verify the compliance of each patient to the physician-prescribed weightbearing and activity restrictions in the mild and moderate restriction groups. In the severe restriction group, some element of compliance is given with casting, while prescribed A-frame braces contain a temperature sensor to monitor the amount of time the brace is worn each day. We observed a strong association between the weightbearing/activity restriction regimen prescribed and patients' reported mobility scores,

suggesting overall good compliance. Second, although the weightbearing and activity restriction regimen prescribed to the patient was performed based on criteria explained in the methods, the determination is largely at the discretion of the practitioner and the author responsible for categorizing the regimen for study purposes. Currently, there is no consensus among the experts on the best or most effective way to treat Perthes disease [14, 23]. Thus, the treatment approach to Perthes disease remains controversial. Various forms of treatment, from symptomatic conservative treatment to Petrie casting and wide abduction bracing to prolonged nonweightbearing with crutches, a walker, or a wheelchair to operative treatments, are recommended by various surgeons and centers. The weightbearing/activity restrictions considered mild or moderate for the purposes of this study are commonly prescribed by surgeons in the early stages of Perthes disease to treat pain, decrease hip irritability, and improve hip motion. Therefore, we believe that the results of this study also have some generalizability outside of our center. As indicated by the low sample size (n = 12), the severe weightbearing and activity restriction regimen is not often used and may only be relevant to select centers that offer Petrie casting and abduction bracing treatments. Third, while PROMIS has been highly regarded as a patient-reported outcome tool, response bias may still occur as patients may unknowingly underreport or overreport their symptoms based on their desired treatment at the clinic visit. Lastly, because of the chronic nature of the disease and to more fully describe the impact of restriction regimens, we would need to observe trends in patient-reported outcomes over time. The study is limited by its cross-sectional nature, but as more chronologic data are compiled, we hope to address this in future research.

Association of Weightbearing and Activity Restrictions and Physical Health

We found that patients treated with more severe weightbearing and activity restrictions were associated with worse mobility, but there was no association with pain interference or fatigue. As expected, more severe weightbearing and activity restrictions were associated with worse mobility scores. This is supported by a small study by Matos et al. [29] from Brazil which found no difference between Perthes disease patients (age > 8 years) and age-matched healthy controls (n = 12/group) in the Physical Function scales using the PedsQL 4.0 questionnaire. In addition, the patients in earlier Waldenstrom stages (Stages I and II) were associated with higher pain interference scores than those in the Stage III. Since the pain interference measure is designed to assess how pain impedes patients' daily activities, this finding is expected. In general, patients are more symptomatic in the earlier stages of Perthes disease and their activities are more impeded by pain [26]. Finally, the scores for the fatigue measure were not associated with weightbearing/activity restriction regimens. Weightbearing/activity restrictions may prevent patients from doing much physical activity, so they do not feel fatigued. On the other hand, in a study by Leo et al. [27], 12 children with Perthes disease (mean age 7 ± 4 years), regardless of disease stage and treatment, completed open-ended questionnaires while their parents were interviewed about the child's quality of life. In one interview, a mother of a patient with Perthes disease reported that her 12-year old son's constant limping led to tiredness, which prevented further activity.

Association of Weightbearing and Activity Restrictions and Mental Health

It was surprising to find that weightbearing and activity restrictions were not associated with patients' depressive symptoms or anxiety scores. Our theory was that more severe weightbearing and activity restrictions would be associated with worse patient-reported

depressive symptoms and anxiety levels. Hailer et al. [9] reported a higher risk of clinical depression from a national registry of patients previously diagnosed with Perthes disease and suggested this may be due to their chronic pain, the inability to participate in physical activities, and the prolonged nature of the disease with uncertain outcomes. However, our results were consistent with previous Perthes disease studies assessing emotional outcomes using questionnaires [8, 29]. In the study by Matos et al. [29], which compared 12 children with Perthes disease older than 8 years to healthy, similarly-aged controls using the PedsQL 4.0 questionnaire, there was no difference in the Emotional Functioning scale between the Perthes disease and control group. Meanwhile, another study by Hailer et al. [8] included 116 patients who were treated for Perthes disease at a single institution and who were nearly all adults completed the standardized EQ-5D-3L health-related quality of life questionnaire. The authors found no substantial differences in the anxiety/depression dimension compared with the general Swedish population. In contrast to our study, patients in both studies completed the questionnaires either by telephone or interview, rather than the patient independently self-completing the questionnaires. Nonetheless, these results may be explained by the fact that patients with Perthes disease, like other children with chronic diseases, frequently endure long periods of variable and unpredictable levels of pain and impairment [4, 7]. As a result, patients often make psychological adjustments, form coping mechanisms, and develop resilience in the face of chronic adversity [4, 27, 33, 41]. Multivariate analysis revealed that female gender was associated with worse depressive symptoms. Although there is no gender difference in the prevalence of depression in childhood, females are twice as likely on average to develop lifetime depression than males, where the difference reportedly starts in

adolescence around age 13 [10, 38].

Association of Weightbearing and Activity Restrictions and Social Health

Another surprising finding was that social health, as evaluated using the peer relationships measure, showed no association with the weightbearing/activity restriction regimen. Our findings are similar to the study by Matos et al. [29] comparing Perthes disease patients with healthy age-matched controls, which found no difference between the two groups on the Social Functioning scale from the PedsQL 4.0 questionnaire. The PedsQL asks questions about feeling isolated, difficulty getting support from others, and finding time or energy for social activities. Additionally, we found that the female gender and earlier age at diagnosis of Perthes disease were associated with lower peer relationships scores. It is possible that females and younger patients feel more isolated due to Perthes disease, which limits them from participating in social activities. Given the small sample size of the study by Matos et al. [29], however, the authors did not specifically assess gender and the age at diagnosis in their analysis. Meanwhile, parents interviewed in the study by Leo et al. [27] reported that peers of Perthes disease patients have assisted patients around the classroom or involved patients in activities that do not have a physical requirement. This observation could be explained by the fact that Perthes disease patients undergoing weightbearing restrictions often use noticeable assistive devices, such as a wheelchair, a walker, or crutches. Individuals with a visible physical disability often receive more peer recognition for their problems than individuals with an invisible disability, such as a mental health disorder [39]. Nonetheless, even patients who did not require assistive devices and were only restricted from running and jumping had similar peer relationship scores to those who used assistive devices.

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

In summary, weightbearing and activity restriction treatments are associated with poorer patient-reported mobility in the active stages of Perthes disease, after controlling for Waldenstrom stage, gender, age of diagnosis, and history of surgery. Additionally, weightbearing/activity restrictions are not associated with pain interference, fatigue, depressive symptoms, anxiety, and peer relationships. These treatments, and our understanding of their association with Perthes disease patients' quality of life, can aid in decision-making for providers, help set expectations for patients and their parents, and provide opportunities for better education and preparation. Future studies may aspire to examine the longitudinal trends of patient-reported outcomes to better understand how this chronic disease impacts children's lives over time.

LIST OF TABLES

Table 1. Demographics of the activity or weightbearing regimen groups

Parameter	No restriction (n = 36)	Mild restriction (n = 27)	Moderate restriction (n = 25)	Severe restriction (n = 12)	Cohen's f^2 or Chi-square	p value
Age at time of diagnosis (median [range] in years)	6 (2 to 12)	7 (3 to 12)	9 (4 to 13)	8 (6 to 13)	$f^2 = 0.28$	< 0.001[a]
Age at time of survey (median [range] in years)	9 (8 to 14)	9 (8 to 14)	10 (8 to 13)	9 (8 to 14)	$f^2 = 0.02$	0.58
Gender (% [n])	M: 97% (35) F: 3% (1)	M: 74% (20) F: 26% (7)	M: 84% (21) F: 16% (4)	M: 75% (9) F: 25% (3)	$X^2 = 7.71$	0.05
Waldenstrom stage (% [n])	Stage I: 3% (1) Stage II: 0% (0) Stage III: 97% (35)	Stage I: 11% (3) Stage II: 8% (2) Stage III: 81% (22)	Stage I: 24% (6) Stage II: 20% (5) Stage III: 56% (14)	Stage I: 8% (1) Stage II: 25% (3) Stage III: 67% (8)	$X^2 = 18.55$	0.005[b]
Lateral pillar class (% [n])	B: 56% (20) C: 44% (16)	B: 30% (8) C: 63% (17)	B: 44% (11) C: 36% (9)	B: 42% (5) C: 42% (5)	$X^2 = 3.79$	0.29
Prior major surgery (% [n])	31% (11)	33% (9)	52% (13)	50% (6)	$X^2 = 3.83$	0.28

[a]There was a difference in the median age at diagnosis among the four weightbearing/activity restriction groups ($p < 0.001$).
[b]There was an association between Waldenstrom stage and the four weightbearing/activity restriction groups ($p = 0.005$).

Table 2. Mean PROMIS scores for each measure and effect size between weight-bearing/activity restriction groups.

PROMIS measure	No restriction (n = 36)	Mild restriction (n = 27)			Moderate restriction (n = 25)			Severe restriction (n = 12)		
	Mean T-score ± SD	Mean T-score ± SD	Mean difference vs No restriction (95% CI)	p value for Mild vs None[a]	Mean T-score ± SD	Mean difference vs No restriction (95% CI)	p value for Moderate vs None[a]	Mean T-score ± SD	Mean difference vs No restriction (95% CI)	p value for Severe vs None[a]
Mobility	53 ± 9	37 ± 5	16 (10, 20)	<0.001[a]	32 ± 8	21 (15, 26)	<0.001[a]	27 ± 9	26 (19, 33)	< 0.001[a]
Pain interference	44 ± 11	51 ± 10	-7 (-13, 1)	0.13	50 ± 11	-6 (-13, 2)	0.22	53 ± 11	-9 (-18, 1)	0.12
Fatigue	38 ± 9	42 ± 10	-4 (-11, 2)	0.34	39 ± 12	-1 (-8, 6)	0.99	42 ± 12	-4 (-13, 5)	0.68
Depressive symptoms	41 ± 8	43 ± 8	-2 (-8, 3)	0.70	44 ± 9	-3 (-8, 3)	0.65	40 ± 10	-1 (-6, 8)	0.97
Anxiety	41 ± 11	44 ± 10	-3 (-10, 5)	0.79	44 ± 13	-3 (-10, 5)	0.84	42 ± 9	-1 (-10, 9)	>0.99
Peer relationships	57 ± 9	53 ± 10	-4 (-3,11)	0.44	52 ± 11	-5 (-2,12)	0.25	57 ± 12	0 (-10, 8)	>0.99

[a]The mean T-scores of the mild ($p<0.001$), moderate ($p<0.001$), and severe restriction ($p<0.001$) groups were lower than that of the no restriction group.

Table 3. Multivariate regression analysis of variables of interest associated with PROMIS® outcomes

Variables	Significantly associated PROMIS outcomes	β regression coefficient (95% CI)	p-Value
Weight-bearing/activity restriction	Physical Function – Mobility a. Mild restriction vs None b. Moderate Restriction vs None c. Severe restriction vs None	 -15 (-19, -10) -19 (-24, -14) -25 (-30, -19)	 <0.001[a] <0.001[a] <0.001[a]
Waldenstrom Stage	Pain Interference a. Waldenstrom Stage I vs III b. Waldenstrom Stage II vs III Peer Relationships (Stage I vs III)	 10 (2, 17) 10 (2, 17) -8 (-15, -1)	 0.01[b] 0.02[b] 0.03[b]
Gender (Female vs Male)	Depressive Symptoms Peer Relationships	7 (2, 12) -6 (-12, 0)	0.005[c] 0.04[c]
Age at diagnosis	Peer Relationships	1 (0, 2)	0.03[d]
History of surgery	None	-	-

[a]The mild ($p<0.001$), moderate ($p<0.001$), and severe ($p<0.001$) restriction groups were associated with worse mobility scores than the no restriction group; [b]Waldenstrom stage I ($p=0.01$) and stage II ($p=0.02$) were associated with worse pain interference scores compared to the Waldenstrom stage III. Waldenstrom stage I was associated with worse peer relationships scores compared to Waldenstrom stage III ($p=0.03$); [c]Females were associated with worse depressive symptoms ($p=0.005$) and peer relationships ($p=0.04$) than males; [d]A younger age at diagnosis ($p=0.03$) was associated with worse peer relationships scores.

LIST OF FIGURES

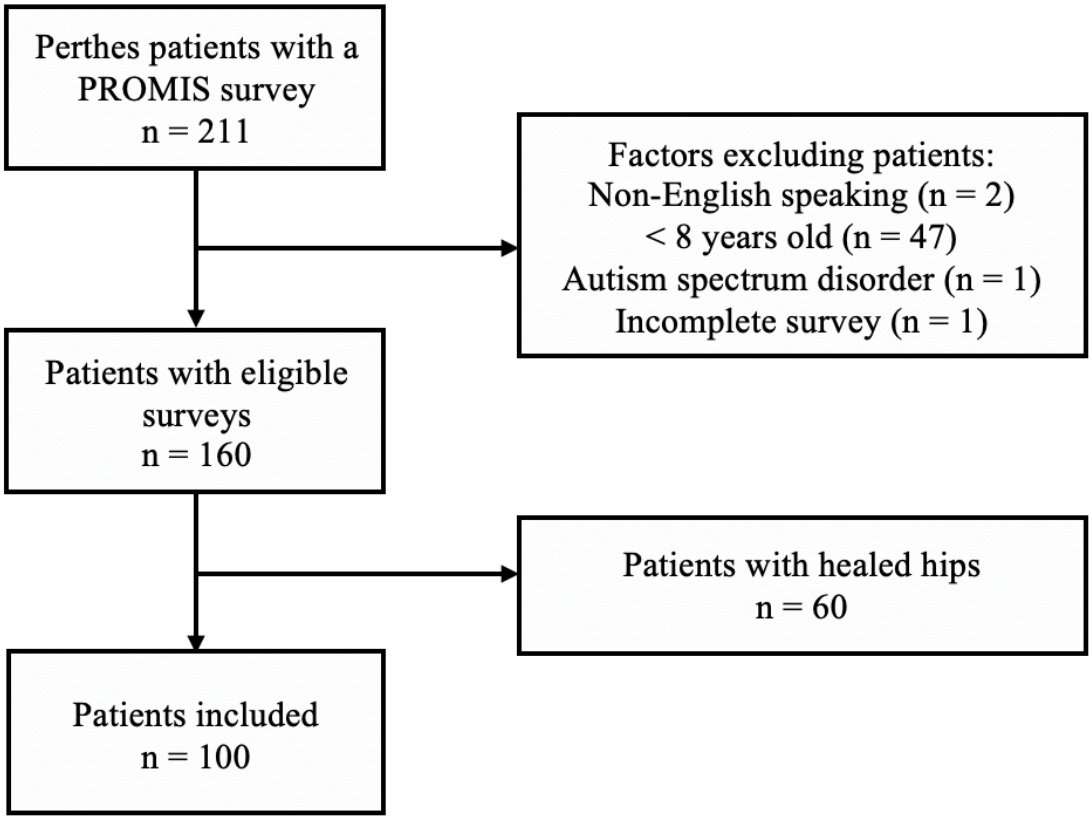

Fig. 1 This flow chart shows the study participants and the exclusion criteria.

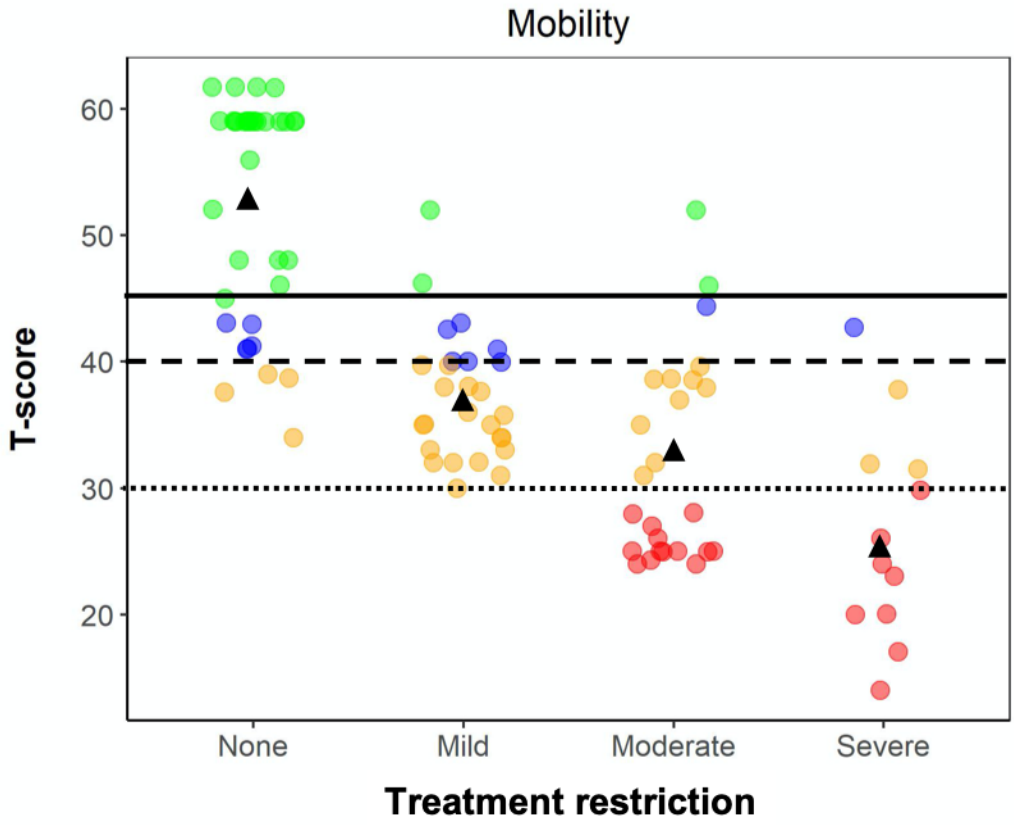

Fig. 2 This graph shows the distribution of mobility T-scores for each of the four weightbearing or activity restriction groups. The triangles indicate the mean T-score for each weightbearing or activity restriction group. Values above the solid line (green dots) are in the normal range. The dashed line indicates the lower cutoff for the mildly abnormal range. The dotted line indicates the lower cutoff for the moderately abnormal range. Values below the dotted line (red dots) are in the severely abnormal
range.

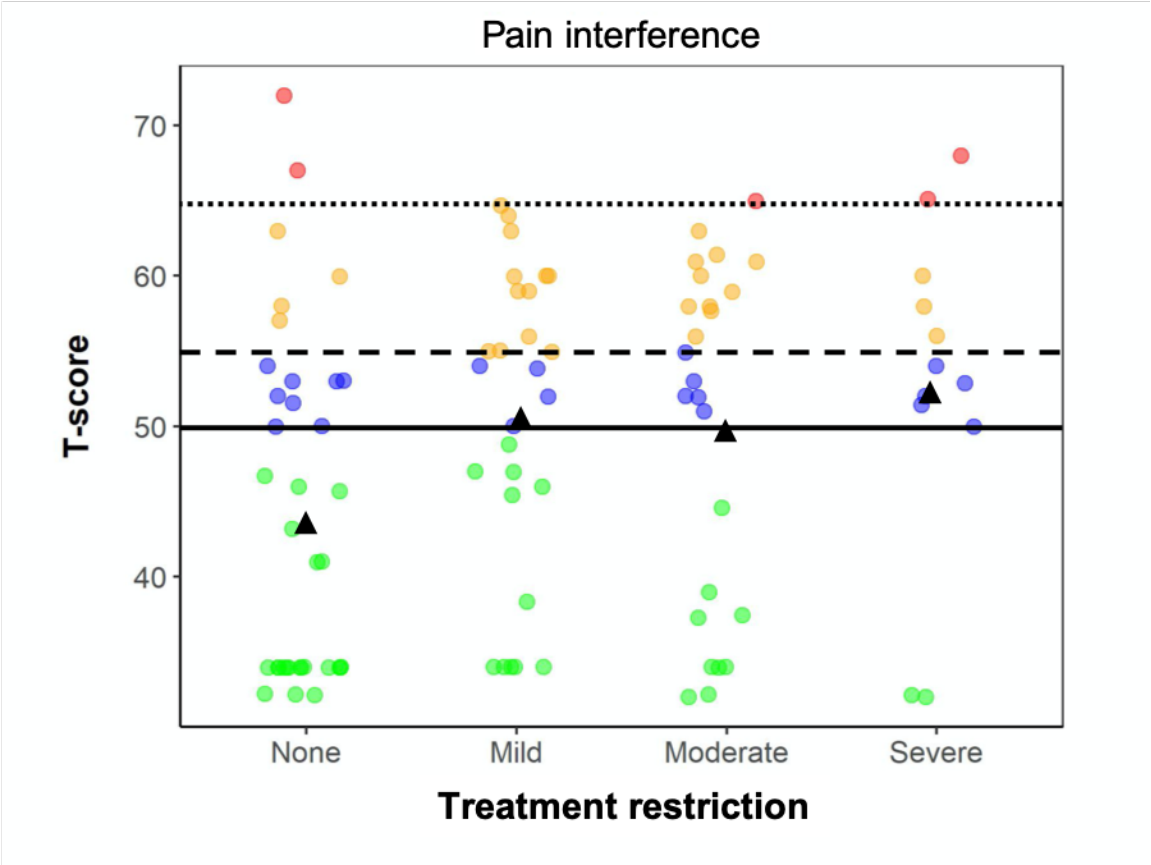

Fig. 3 This graph shows the distribution of pain interference T-scores for each of the four weightbearing or activity restriction groups. The triangles indicate the mean T-score for each weightbearing or activity restriction group. Values below the solid line (green dots) are in the normal range. The dashed line indicates the upper cutoff for the mildly abnormal range. The dotted line indicates the upper cutoff for the moderately abnormal range. Values above the dotted line (red dots) are in the severely abnormal range.

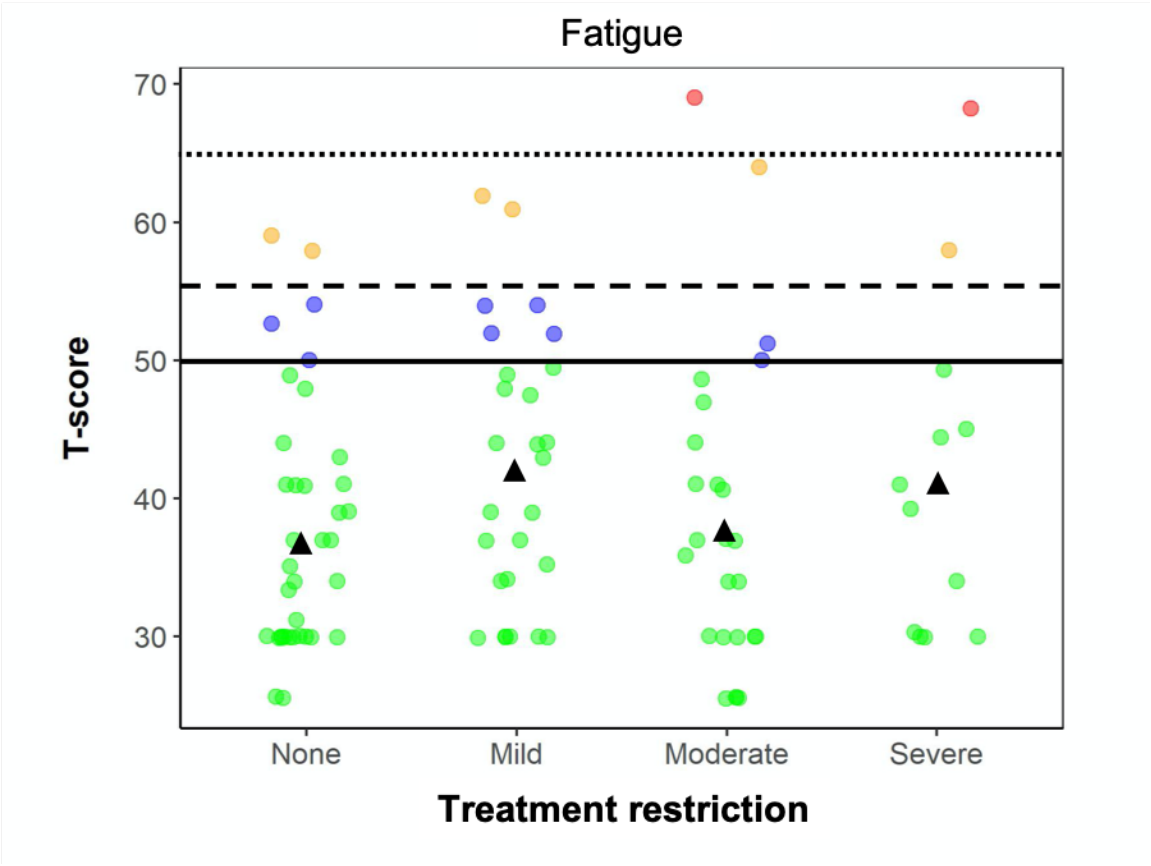

Fig. 4 This graph shows the distribution of fatigue T-scores for each of the four weightbearing or activity restriction groups. The triangles indicate the mean T-score for each weightbearing and activity restriction group. Values below the solid line (green dots) are in the normal range. The dashed line indicates the upper cutoff for the mildly abnormal range. The dotted line indicates the upper cutoff for the moderately abnormal range. Values above the dotted line (red dots) are in the severely abnormal range.

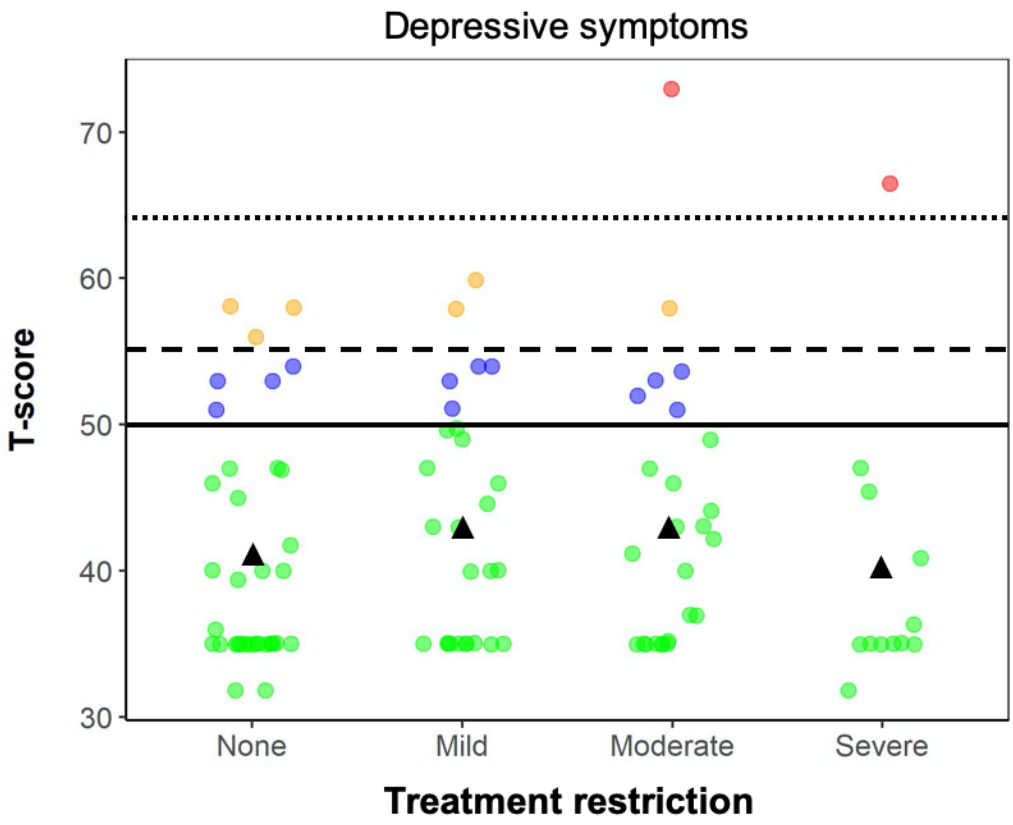

Fig. 5 This graph shows the distribution of T-scores for depressive symptoms for each of the four weightbearing or activity restriction groups. The triangles indicate the mean T-score for each weightbearing or activity restriction group. Values below the solid line (green dots) are in the normal range. The dashed line indicates the upper cutoff for the mildly abnormal range. The dotted line indicates the upper cutoff for the moderately abnormal range. Values above the dotted line (red dots) are in the severely abnormal range.

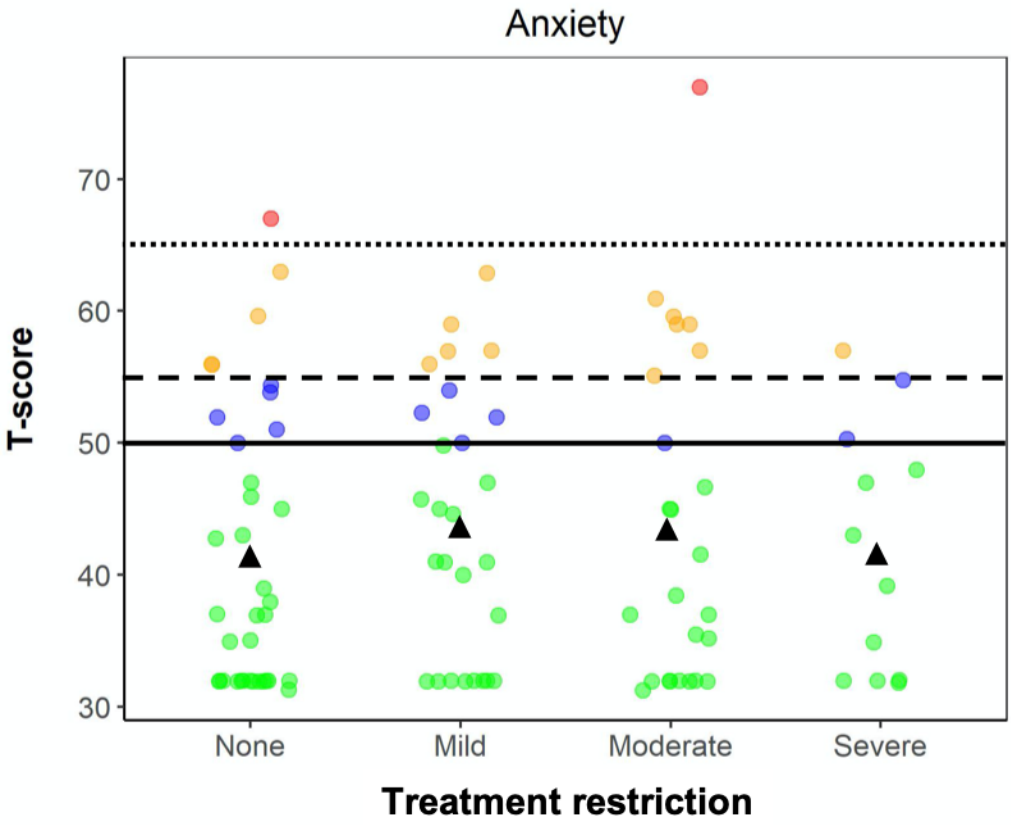

Fig. 6 This graph shows the distribution of anxiety T-scores for each of the four weightbearing or activity restriction groups. The triangles indicate the mean T-score for each weightbearing or activity restriction group. Values below the solid line (green dots) are in the normal range. The dashed line indicates the upper cutoff for the mildly abnormal range. The dotted line indicates the upper cutoff for the moderately abnormal range. Values above the dotted line (red dots) are in the severely abnormal range.

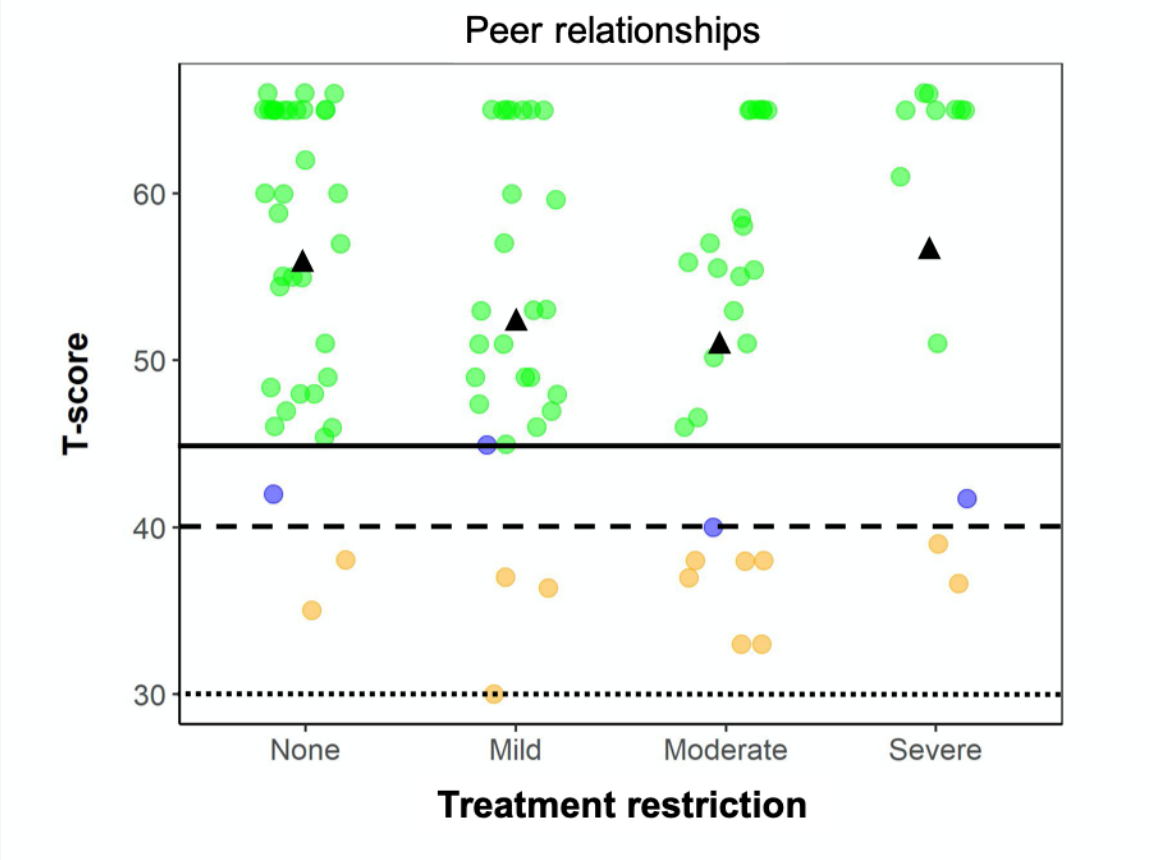

Fig. 7 The graph shows the distribution of peer relationships T-scores for each of the four weightbearing or activity restriction groups. The triangles indicate the mean T-score for each weightbearing or activity restriction group. Values above the solid line (green dots) are in the normal range. The dashed line indicates the lower cutoff for the mildly abnormal range. The dotted line indicates the lower cutoff for the moderately abnormal range. There were no values below the dotted line, which indicates the severely abnormal range.

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