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Prospective Mediation Models of Sleep, Pain and Daily Function in Children with Arthritis using Ecological Momentary Assessment

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Abstract

Objectives—Sleep is an emerging area of concern in children with juvenile idiopathic arthritis (JIA). Research shows the presence of poor sleep quality and related adverse outcomes in pediatric pain populations, including JIA, but few studies have examined the prospective patterns of association between sleep and associated outcomes. This prospective study evaluated the direction and magnitude of associations between subjective sleep characteristics (sleep quality, difficulty initiating sleep, and sleep duration), pain intensity, and functional limitations in children with JIA. We hypothesized that pain intensity would partially mediate the relationship between sleep and functional limitations.

Methods—Children and adolescents with JIA (n= 59, age range = 8–18) recruited during clinic visits, completed smartphone-based diaries for one month. Subjective sleep characteristics were reported each morning; pain and functioning were assessed three times daily.

Results—As hypothesized, the associations between sleep quality and functional limitations and between difficulty initiating sleep and functional limitations were partially mediated by pain intensity, at any given moment ($z = -3.27$, $p = .001$, $z = 2.40$, $p < .05$). Mediation was not detected in a model testing the association between sleep duration, pain intensity, and functional limitations ($z = -.58$, $p = .56$).

Discussion—Results suggest that sleep is integral to understanding the momentary association between pain intensity and functioning in children with JIA.

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Keywords

Pain; sleep; functioning; electronic diaries; juvenile arthritis

Introduction

In juvenile idiopathic arthritis (JIA) and other chronic pain conditions of childhood, the importance of assessing both pain and functional limitations is well described.^{1–3} Childhood chronic pain adversely affects physical, social, and school functioning. Indeed, reducing the impact of pain on daily functioning is a key multimodal pain management objective.⁴ Despite recent advances in pharmacotherapy that dramatically improve disease control in children with JIA, other electronic diary (e-diary) findings showed continued daily pain, stiffness, fatigue, and associated functional limitations.⁵ We also previously demonstrated that emotion regulation is an important predictor of both pain and function in this sample.⁶ Identifying other factors underlying or maintaining both pain and impaired function in JIA is necessary to guide innovations in nonpharmacological treatments. Sleep is a modifiable behavior that may be uniquely important in pediatric chronic pain. Indeed, studies have shown that over 50% of children with pediatric chronic pain experience poor sleep quality and/or insomnia symptoms (e.g., difficulties initiating and maintaining sleep),^{7, 8} but few studies have examined daily subjective sleep reports in relation to both pain and functioning. This study was conducted to determine the prospective role of subjective aspects of sleep in daily pain and functioning of children with JIA.

Recently, focus on the role of sleep in the maintenance and outcomes of chronic pain conditions has increased.⁹ In adults, disrupted sleep contributes to pain sensitization¹⁰ and lost productivity.¹¹ In childhood and adolescence, disrupted sleep impacts cognitive, emotional, academic, and social/emotional functioning¹² and is increasingly recognized as an important variable in understanding pediatric chronic pain.¹³ Sleep affects pain via various physiological or psychosocial pathways;^{9, 14} for example, poor sleep quality may influence mood or coping, which in turn affect pain perception and functioning.

A limitation of most studies examining the sleep-pain association to date is that they have employed cross-sectional methods, precluding a nuanced characterization of the association. Even past daily diary research has relied on *end-of-day* pain intensity ratings,^{7, 15, 16} prompting children to reflect back on symptoms during the day, thereby, preventing examination of concurrent symptoms. Further, only one prior pediatric study incorporated functional limitations into sleep-pain models,¹⁷ despite the role of functional limitations as a critical treatment outcome variable in chronic pain¹⁸ and JIA.¹⁹ A recent review of sleep in pediatric chronic pain populations explicitly recommended including functional limitations in studies of sleep and pain.¹³

Children and adolescents' comfort and familiarity with technology affords new strategies for tracking symptoms and behaviors *in-the-moment*. Such methodology has been employed in studies of daily pain, health behaviors, daily stress, and psychopathology symptoms.^{20–23} Prospective data collection is essential for nuanced understanding of complex, temporal relationships and avoids many pitfalls of paper diaries (e.g., backfilling data, retrospective

bias) by employing features (e.g., alarms, data locking, automated uploading) to promote accurate data collection.

The current study used e-diaries to test prospective temporal associations between sleep, pain, and functioning in children with JIA based on Valrie and colleagues¹³ theoretical pediatric sleep-pain model. We hypothesized that pain intensity ratings would mediate the relationship between self-reported sleep characteristics (sleep quality, difficulty initiating sleep, and sleep duration) and overall functional limitations in children with JIA. Specifically, we expected to find that lower sleep quality, shorter sleep duration, and greater difficulty initiating sleep predict higher functional limitations, and that these momentary associations would be partially accounted for by concurrent pain intensity. We did not expect to find full mediation in any tested model, given that poor sleep is known to have direct adverse effects on daytime functioning in healthy children in the absence of pain.

Materials and Methods

Participants and Procedure

The current study was conducted as part of a larger investigation (R01HD053431) of daily symptoms and behaviors in children with JIA. Previous publications examined medication class⁵ and child emotion regulation⁶ in relation to primary pain outcomes (daily symptom reports and functional limitations). Detailed descriptions of the sample and reporting patterns are available in Bromberg et al.⁵ This study extends on previous studies using this dataset by uniquely examining sleep, which was an ancillary aim of the larger project and not included in previous papers.

The Duke University Medical Center Institutional Review Board approved all study procedures. Patients in the pediatric rheumatology clinic were pre-screened for eligibility based on medical records review. Children were eligible to participate based on the following criteria: 1) between the ages of 8–18 years, and 2) meeting International League of Associations for Rheumatology (ILAR) diagnostic criteria for juvenile idiopathic arthritis with polyarticular presentation.²⁴ Children were ineligible if they were diagnosed with another major medical or psychiatric condition that could affect pain or were not currently enrolled in a formal academic curriculum, or if they or their parent had low English or computer literacy on screening. Informed consent was obtained from parents and consent or assent was obtained from child participants during a routine visit to the Duke Pediatric Rheumatology Clinic. All e-diary data collection took place during the academic school year.

Following informed consent, children and parents completed baseline questionnaires and were trained to use the T-Mobile® Dash smartphone and to complete e-diaries via a custom mobile application. In-person training, including completing sample diaries with the study coordinator, was conducted to ensure that all participants could navigate the provided smartphone and could complete diary entries. Families selected times to enter 3 daily e-diaries (upon waking, after school, before bedtime) based on their typical routines. Research staff programmed automatic emails to sound an alert on the smartphone to prompt for data entry at the selected times. E-diaries were accessible for completion only at the appropriate

time of day and access was subsequently locked to prevent backfilling of missed entries. Families were provided a procedures manual, an individualized study calendar, and a prepaid mailer for returning the smartphone. Entries were wirelessly transmitted to a secure database once completed. Research staff monitored daily completion and contacted participants to problem-solve if completion rates declined.

Similar to other daily diary studies,^{23, 25, 26} incentives were employed to promote entry completion. For the first two weeks of the study, participants earned \$0.25 for each e-diary entry. Participants earned \$0.50 for each e-diary entry completed during the last two weeks of the study, in order to promote ongoing participation. Participants also earned \$0.50 bonuses for completing 3 reports in one day and \$1.25 bonuses for each full week of e-diary entries. A gift card loaded with the total amount was given to each participant at the end of the study.

Electronic Diary

E-diaries have been validated for prospectively assessing juvenile arthritis pain.²⁷ The e-diary format, including sleep and pain content was adapted from previous paper diaries.^{26, 28–30} E-diary items assessing sleep quality during the past night, current pain intensity, and current functional limitations were used for analysis in this study.

Sleep—Sleep quality, duration, difficulty initiating sleep, location, and number of night wakings were measured each morning. Subjective aspects of sleep, similar to those characterizing insomnia (difficulty initiating sleep, sleep quality) and sleep duration were selected as the primary sleep variables in analyses in order to capture children's unique experience and perception of sleep from day to day. Sleep quality was rated via a global rating of sleep quality on a 50mm electronic visual analog scale (e-VAS). Children were shown a screen with a horizontal bar half filled with blue, anchored by "did not sleep well" and "slept very well." A warning appeared if the child did not move the bar from the starting location. A similar sleep quality VAS has been used on previous paper diaries,^{16, 26, 28, 31, 32} and scores were converted to a 100 point scale to be comparable to paper diary findings. Children rated their difficulty initiating sleep on the previous night on an item scaled from "0- not very difficult" to "4- extremely difficult." Children selected a sleep duration range between 1 (less than 4 hours), 2 (4–8 hours), 3 (8–10 hours), and 4 (more than 10 hours). Sleep location (e.g., own bed, parent's bed, away from home) and the number of night wakings during the previous night were also captured on each morning diary. Daily sleep logs are a valid and reliable method for assessing sleep^{33, 34} and morning sleep reports capture the subjective sleep experience in the home setting.

Pain Intensity—An e-VAS (50mm in length) was used to assess *current* pain intensity on all e-diaries, anchored by "no pain" and "a lot of pain," with scores converted to a 100 point scale. The pain e-VAS was similar to a validated pain VAS from the Pediatric Pain Questionnaire³⁵ and was based upon those used in paper diaries.^{26, 28} The VAS is a well validated method of assessing subjective pain intensity³⁶ and has been recommended for use in children ages 8 and older.³⁷

Functional Limitations—Functional limitation e-diary items were selected based on a review of validated measures. Items from the Child Activity Limitations Interview^{38, 39} and the Activities Scale for Kids⁴⁰ were selected to assess aspects of functioning across physical, social, and school domains. Both scales are valid measures of functional limitations and have adequate psychometrics. The adapted e-diary activity limitation items demonstrated good to excellent reliability, as previously reported.⁶ Functional limitation items varied across morning, afternoon, and evening e-diaries; the 8 items appearing on each e-diary were selected to be most relevant for the time of day. For example, an item regarding getting dressed appeared only on the morning e-diary and items assessing school functioning appeared only on the afternoon and evening e-diaries. Response options ranged from “1- not very difficult” to “4- extremely difficult.” A total functional limitations score was derived for each entry by summing across all functional limitation items on each e-diary.

Disorders of Initiating and Maintaining Sleep

During the baseline visit, parents completed the Sleep Disturbance Scale for Children (SDSC), a standardized, general screening of sleep problems for children and adolescents. Parents are asked to rate the frequency of each sleep disturbance (e.g., “The child goes to bed reluctantly,” “you have observed the child sleepwalking”) on a scale of 1 (never) to 5 (always, daily). The SDSC results in six subscales, including disorders of initiating and maintaining sleep (DIMS), which assesses symptoms of insomnia. The DIMS subscale was used in this study to further describe insomnia symptom scores and to validate the sleep items. Each subscale score is converted to a T-score. The SDSC is a valid and reliable assessment of pediatric sleep disturbances.⁴¹

Demographics

Parents completed an electronic questionnaire assessing child demographics via a secure study website. A pediatric rheumatologist provided a rating of disease activity on a 4-point scale ranging from 0 (inactive) to 3 (severe) based on findings from a routine clinical examination. This method of classifying JIA disease activity is frequently used in clinical research.

Data Analysis

Hypothesis testing was conducted via multilevel modeling techniques, which are well suited and recommended for quantitative analysis of daily diary data.⁴² This analytic strategy accommodates missing data and the collinearity of measures repeated within a short period of time and offers the opportunity to examine patterns of association both momentarily (within-child) at “level 1” and typically (between-child) at “level 2,” while holding estimated error variability constant. Simulations indicate that data from at least 50 participants are necessary to avoid biased estimates of standard errors;⁴³ our sample of 59 children with at least 25 diary entries resulted in 3258 unique diary entries for analysis. Hypothesis testing was completed following Zhang et al.⁴⁴ procedures testing 1-1-1 multilevel mediation using the centered within context with reintroduction of the subtracted means (CWC(M)) approach, which consists of a series of model testing to obtain parameter estimates. Per these guidelines, significance testing was conducted via a Sobel test,⁴⁵ using

an online calculator.⁴⁶ This approach allows mediation testing at both model levels to avoid confounding effects when interpreting findings regarding the hypothesized momentary, level 1, within-child effects. Additional methods of hypothesis testing (e.g., parametric bootstrapping) were not performed due to the small p values detected using the Sobel test for mediation.

Results

Descriptives

Data completeness and demographics—Data from 59 participants (83% of participants enrolled in the larger study who completed any study measures) were analyzed, based on criteria of completing 25 e-diary entries. Of the retained sample, individual completion rates ranged from 25–91 entries ($m = 56.2$, $SD = 18.4$), with a total of 3258 entries across all participants and a 66% completion rate. Number of e-diary entries was not related to sex ($F(1, 56) = 5.94$, $p = .44$), physician-rated disease activity ($F(3, 51) = .10$, $p = .96$), or age ($r = .06$, $p = .63$). Participant demographics were consistent with the clinic population, being primarily Caucasian (73%) and female (74%) with mild (43.1%) or moderate (39.7%) disease activity. The average age of participants was 13.3 years ($SD = 2.8$). Medication use patterns were previously described⁵ and medication class was largely not associated with pain intensity, sleep quality, sleep difficulty, or activity limitations. The exception to this pattern of findings was that children prescribed disease modifying antirheumatic drugs (DMARDs) had higher average activity limitations than children not prescribed DMARDs, ($t(56) = 3.24$, $p < .01$).

Sleep descriptives—There was a moderate negative correlation between average sleep quality scores and DIMS scores ($r = -.39$, $p < .01$) and a moderate positive correlation between average sleep difficulty ratings and DIMS scores ($r = .32$, $p < .05$), supporting the validity of the sleep diary items for assessing aspects of insomnia. Children reported moderately high sleep quality ($m = 67.9$, $SD = 27.4$) when averaged across all diary days, similar to previous sleep quality reports in children with JIA¹⁵. Participants reported difficulty initiating sleep during the night before on 29% of study days. Developmentally, children in the sample age range require somewhere between 8–10 hours of sleep per night; in this sample, children reported obtaining greater than 8.0 hours of sleep per night on only 41% of all study nights. Children reported very short sleep (0–4.0 hours) on 7% of nights. There was a strong, negative correlation between sleep quality and sleep difficulty ($r = -.54$, $p < .001$) and sleep quality and number of night wakings ($r = -.46$, $p < .001$), and there was a moderate positive correlation between sleep quality and sleep duration ($r = .36$, $p < .001$).

Children recalled few night wakings on the morning diaries; no wakings during the night were reported on 56% of diary entries and 1–3 wakings were reported on 36% of diaries. Children reported sleeping in their own bed the majority of study days (83%), and reported sleeping with another family member (parent or sibling) on 13% of nights during the study. On the SDSC, 29% of participants had elevated insomnia symptom scores on the DIMS subscale (T scores > 70).

Pain and functioning descriptives—As previously reported⁵, average pain intensity was in the mild to moderate range ($m = 26.3$, $SD = 27.5$) and there were no significant differences in pain intensity across morning, afternoon, and evening reports. Children in this sample reported mild functional limitations ($m = 3.9$, $SD = 7.3$, range = 0–32) on average. A subgroup of children reported average pain intensity in the severe range and all children endorsed pain during the reporting period.

Concurrent Associations between Sleep, Pain Intensity, and Functional Limitations

Figure 1 displays the results of multilevel mediation analyses testing the effects of *sleep quality* on functional limitations and whether this association is mediated by momentary pain intensity. As hypothesized, there was a direct inverse within-child relationship between sleep quality and functional limitations ($\beta = -.03$, $p < .001$) and a direct positive within-child relationship between pain intensity and functional limitations ($\beta = .11$, $p < .001$). Pain intensity increased at times when sleep quality was lower ($\beta = -.07$, $p < .001$). The result of the Sobel test for level 1 mediation was significant ($z = -3.27$, $p = .001$), supporting an indirect relationship between sleep quality and functional limitations mediated by pain intensity. However, the direct relationship between sleep quality and functional limitations remained significant when accounting for momentary pain intensity ($\beta = -.02$, $p < .001$). Thus, pain intensity mediates the association between sleep quality and functional limitations but does not fully account for this relationship.

Figure 2 displays the results of multilevel mediation analyses testing the effects of *sleep difficulty* (i.e., difficulty initiating sleep at bedtime) on functional limitations and whether this association is mediated by momentary pain intensity. As hypothesized, there was a direct within-child relationship between sleep difficulty and functional limitations ($\beta = .88$, $p < .001$) and a direct positive within-child relationship between pain intensity and functional limitations ($\beta = .08$, $p < .001$). Pain intensity increased at times when sleep difficulty was higher ($\beta = 2.07$, $p < .05$). The result of the Sobel test for level 1 mediation was significant ($z = 2.40$, $p < .05$), supporting an indirect relationship between sleep difficulty and functional limitations mediated by pain intensity. However, the direct relationship between sleep quality and functional limitations remained significant when accounting for momentary pain intensity ($\beta = .78$, $p < .001$). Thus, similar to findings for sleep quality, pain intensity mediates the association between sleep difficulty and functional limitations but does not fully account for this relationship.

Figure 3 displays the results of multilevel mediation analyses testing the effects of *sleep duration* on functional limitations and whether this association is mediated by momentary pain intensity. A different pattern of findings emerged for sleep duration, compared to the findings in models testing sleep quality and difficulty. While there was a direct negative association between sleep duration and functional limitations, ($\beta = -.09$, $p < .001$) and a direct positive within-child relationship between pain intensity and functional limitations ($\beta = .08$, $p < .001$), there was not a direct association between sleep duration and pain intensity ($\beta = 0.54$, $p > .56$) and pain intensity did not mediate the association between sleep duration and functional limitations ($z = -.58$, $p = .56$).

Discussion

This study aimed to test the associations between pain intensity, sleep characteristics, and daily functioning in children with JIA. We hypothesized that momentary pain intensity ratings would partially account for the relationship between sleep characteristics and concurrent momentary functional limitations. Using advanced data collection methods and statistical techniques, the present study found that youth with JIA reported greater functional difficulties during days following nights of poorer perceived sleep quality. Further, study results suggested that the association between sleep quality and functional limitations was partly mediated by pain intensity; lower sleep quality was related to higher pain intensity, which in turn was related to higher functional limitations at any given moment during the day.

A similar pattern of findings was detected for difficulty initiating sleep: Greater reported difficulty falling asleep was directly associated with greater functional limitations, but this relationship was partly mediated by higher pain intensity. In contrast, while self-reported estimates of lower sleep duration were directly associated with higher functional limitations, this association was not mediated by pain intensity; sleep duration was not associated with pain intensity ratings. This finding may be due to the sleep duration item used in this study. In order to avoid clock-watching, we chose to use an item with response options that were ranges of sleep duration (e.g., less than 4.0 hours), rather than calculating sleep duration via reported sleep onset and wake times. Unlike sleep quality and difficulty initiating sleep, which are entirely subjective experiences, self-reported sleep duration could be compared to objective estimates of sleep duration (e.g., from actigraphy) in future research.

Previous research has shown that sleep and pain are both associated with functional outcomes, but few studies have tested the temporal associations amongst these factors. Theoretical models¹⁴ and past research have supported a reciprocal association between daily sleep quality and pain intensity in children with chronic pain or JIA, but evidence suggests that the pathway between poorer sleep quality preceding higher pain intensity may be stronger in both children and adults.⁹ Although our previous analyses with this dataset indicated that children and adolescents with JIA continue to experience frequent, moderate intensity pain and daily functional limitations, we had not examined the direction and magnitude of prospective associations between pain intensity, sleep, and functional limitations. The findings of the present study suggest that pain intensity should not be considered in isolation when predicting functional limitations; while pain intensity explained some of the association between sleep and functional limitations, poor sleep quality and difficulty falling asleep also uniquely contributed to both higher pain intensity and higher functional limitations. Together with other research on the role of sleep in the context of chronic pain,^{9, 13, 47} findings from this study underline the central importance of sleep as a key part of the daily chronic pain experience. Results of this study also imply that interventions aimed at improving sleep may be important in JIA.

These findings are congruent with accumulating evidence stressing the need to promote optimal sleep in children with chronic painful conditions.¹³ Disrupted sleep affects daytime functioning across multiple domains in all children^{48, 49} and our findings suggest that sleep

quality and difficulty initiating sleep are prospectively related to both pain intensity and functional limitations. Impact on daily functioning is a marked clinical concern for the families of children with JIA and other chronic pain conditions and as such treatments that promote optimal functioning are an essential part of overall disease management. Future research should expand this line of inquiry to investigate other biopsychosocial factors moderating or mediating the detected associations between pain intensity, sleep, and functioning to better understand how and why sleep influences daily pain and functioning. Other proposed variables include biological (inflammation, dopaminergic and opioidergic signaling), pharmacological (sleep-modifying agents), and psychosocial factors (affect, cognitions, socio-contextual factors).^{9, 13}

There are several limitations to consider when interpreting the study findings. The recruited participants represent a sample of convenience, largely composed of Caucasian females with minimal to mild disease activity. While these demographics are reflective of the clinical population of children with JIA, and participants endorsed frequent, sometimes severe pain, these findings may not generalize to patients with more active JIA. In addition, completion rates for the daily diaries appeared to vary at random and were not seemingly a function of demographics or other variables measured in this study; in the future it may be important to assess factors related to the technological demands of the employed data collection method, such as familiarity/comfort with technology or technical difficulties. It is also possible that medications used to treat JIA influence sleep; however, there has been limited research on the effects of these medications on sleep.⁵⁰ The few studies in adults to examine biologic agents, DMARDs or nonsteroidal anti-inflammatory drugs (NSAIDs) and sleep have detected no associations. Additional research is needed to determine the effects of DMARDs, NSAIDs, and other medications commonly used in treating JIA on sleep in order to guide inclusion in future statistical models.

In addition, while the self-reported sleep items captured via daily diary are characteristic of insomnia, in the absence of physiological sleep assessment (e.g., polysomnography), it is unclear if the sleep disturbances captured in this study are purely behavioral or if an underlying sleep disorder (e.g., sleep disordered breathing, restless leg syndrome) contributed to participant ratings. Additionally, average sleep quality ratings and sleep difficulty ratings were strongly correlated, suggesting that sleep quality ratings may be influenced by how difficult it was to fall asleep, which may account for the similarity of findings for the two models examining these aspects of sleep in the context of momentary pain and functioning. In order to further enhance understanding of the day-to-day sleep of children with JIA in the home setting, future research should incorporate actigraphic assessment of sleep wake patterns, including sleep efficiency, latency, and duration, in conjunction with subjective sleep ratings. More detailed sleep information will lead to a better understanding of the specific aspects of sleep that contribute to daily health outcomes in children with JIA. This will help to clarify findings from previous cross sectional research, which has produced equivocal results regarding the type and role of sleep problems in children with JIA,^{51–53} partially due to differences in measures. However, given that a variety of sleep problems contribute to heightened pain sensitivity,^{54–56} and that subjective rather than objective sleep disturbances have been related to pain,⁵⁷ it was important to use subjective sleep assessment in this study as research in this area continues to develop.

A strength of this study was the use of an e-diary to obtain repeated measures of current symptoms and behaviors with the benefit of prompted reporting, immediate data uploading, and backfilling prevention. The use of mobile tools also holds promise for developing alternate intervention modalities that may be used to intervene on temporal associations as they occur. For example, mobile programs could be used to help children identify factors contributing to disrupted sleep and promote behavioral changes aimed at increasing sleep quality in the child's home environment each day.

Given the findings that subjective daily sleep experiences affect daily pain and functioning in children and adolescents with JIA together with past research on the role of sleep in pediatric chronic pain, in the future it will be important to test sleep-specific interventions. This research is already being conducted in adults, with clinical trials of cognitive behavioral therapy for insomnia (CBT-I) resulting in significant improvements in sleep in adults with chronic pain.^{58–61} Findings are somewhat mixed in regard to improved pain outcomes⁶² and few studies have directly examined functional outcomes following CBT-I interventions. It will be important to test developmentally adapted CBT-I in pediatric trials as a possible approach for promoting optimal pain reduction and improved functioning.

In conclusion, findings from this study highlight the impact of sleep on both daily pain and functioning. Further prospective research is imperative for establishing temporal associations and an empirical basis for future treatment development. Findings preliminarily indicate that sleep-focused interventions may promote improved functional outcomes as well as reductions in pain intensity in children with JIA.

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Figure 1.

* $p < .05$

** $p < .001$

The parameter estimates are for child mean-centered predictors.

The value in parentheses represents the indirect effect of sleep quality on functional limitations via pain intensity

Figure 3.

* $p < .05$

** $p < .001$

The parameter estimates are for child mean-centered predictors.

The value in parentheses represents the indirect effect of sleep duration on functional limitations via pain intensity