Longitudinal Relationships of Depressive Symptoms to Pain Intensity and Functional Disability Among Children with Disease-Related Pain

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Objective To examine the longitudinal relationship between depressive symptoms at study entry (T1) on pain intensity (PI) and functional disability over a 1-year period among children with either sickle cell disease (SCD) or juvenile idiopathic arthritis (JIA). **Methods** 119 children, ages 8–17 years, completed measures of depression at T1 as well as pain and functional disability at T1, 6-month (T2), and 12-month (T3) follow-ups. Caregivers also rated their child's pain and disability at each time point. General linear mixed modeling was employed to examine longitudinal relationships between study variables. **Results** For children with JIA, T1 pain significantly moderated the effects of T1-depressive symptoms on T2 and T3 pain where T1-depressive symptoms predicted future child-reported pain only when T1 pain was relatively mild. Similarly, T1-depressive symptoms predicted future child-reported disability only when initial reports of disability were relatively low. Only family income significantly predicted T2 and T3 pain in children with SCD. **Conclusions** Study findings suggest that T1-depressive symptoms play a role in the longitudinal course of pain symptoms in children with JIA but not in children with SCD.

Key words chronic pain; depression; functional disability; juvenile idiopathic arthritis; sickle cell disease.

Sickle cell disease (SCD) and juvenile idiopathic arthritis (JIA) are two relatively common childhood chronic conditions, affecting 72,000 and 200,000 individuals, respectively, each year in the United States (Cassidy & Nelson, 1988; United States Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, 1996). Both conditions are characterized by disease-related pain episodes. In SCD, pain episodes occur when sickled red blood cells are unable to pass through the narrowest blood vessels, causing an obstruction, reducing blood flow and, subsequently, an accumulation of waste products producing pain called a vaso-occlusive crisis. On average, children and adolescents with SCD experience five to seven vaso-occlusive crises per year (Shapiro, 1993), although in prospective studies, most of the children (65%) have been shown to experience a painful episode over a 2-week period (Gil et al., 2000). In JIA, pain occurs because of tissue inflammation of the musculoskeletal system, blood vessels, and skin (National Institute of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2001). Recent studies have shown that mild to moderate intensity pain is quite common in children with JIA (Anthony & Schanberg, 2003) and occurs on a weekly basis for many children (Schanberg, Anthony, Gil, & Maurin, 2003).

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Journal of Pediatric Psychology 31(10) pp. 1046–1056, 2006
doi:10.1093/jpepsy/jsj076
Advance Access publication September 8, 2005

Pain secondary to chronic disease can be disabling for some children (Palermo, 2000). Functional disability, that is, impairment in performing age-appropriate physical, mental, and social activities in daily life owing to pain, has been documented in children with JIA and SCD (e.g., Anthony & Schanberg, 2003; Palermo, 2000). However, considerable inter-individual variability has been observed with regard to the frequency and intensity of pain and extent of limitations in daily functioning experienced regardless of disease type or severity (Hagglund, Schopp, Alberts, Cassidy, & Frank, 1995; Ilowite, Walco, & Pochaczevsky, 1992). In an attempt to understand the variability in pain perception and pain-related disability, many models have been developed in the adult-pain literature including the biopsychosocial model of pain (Turk & Flor, 1999), the fear and harm avoidance model (e.g., Crombez, Vlaeyen, Heuts, & Lysens, 1999), and self-efficacy model (e.g., Cioffi, 1991). Central to these models are interrelationships among physical, cognitive, affective, and social factors that influence pain and disability outcomes. A significant limitation in the development and testing of such comprehensive models of chronic pain and disability are the predominance of cross-sectional studies that only allow for tests of the association among variables rather than specific tests of temporal or causal relationships. Therefore, the primary purpose of this study is to contribute to this literature by testing the predictive value of one specific construct in the biopsychosocial model of pain, depressive symptomatology, in children with disease-related pain.

Depressive symptoms are consistently associated with pain perception in cross-sectional studies of children with a chronic disease (Sandstrom & Schanberg, 2004). Independent of medical diagnosis, many children and adolescents report concurrent chronic pain and depressive symptoms (e.g., Kashikar-Zuck, Vaught, Goldschneider, Graham, & Miller, 2002). For example, Kashikar-Zuck, Goldschneider, Powers, Vaught, and Hershey (2001) found that depressive symptoms were significantly associated with functional disability scores in children and adolescents with either chronic daily headache or musculoskeletal pain. Findings of this study are particularly striking given that 75% of the children reported functional disability in the moderate to high range (Kashikar-Zuck et al., 2001). Similarly, in a daily diary study with children with JIA conducted by Schanberg et al. (2000), negative mood and increased stressful events were significantly associated with greater activity interference owing to pain.

Few studies have examined risk factors that are longitudinally associated with pain or disability in children, especially in children and adolescents with different chronic conditions in which recurrent pain is a hallmark symptom. Children with chronic disease-related pain may experience changes in pain and disability over time reflective of their disease course, development, and ability to cope. The identification of predictive and prognostic factors could provide new insights for the prevention of chronic-disabling pain and more appropriate treatment and intervention. El-Metwally, Salminen, Auvinen, Kautiainen, and Mikkelsson (2004) examined persistence of musculoskeletal pain in a population-based sample of preadolescents, finding that depressive feelings as well as age, abdominal pain, night time wakenings, and hypermobility predicted pain recurrence at 4-year follow-up in girls, whereas headache, abdominal pain, and having combined musculoskeletal pain predicted pain recurrence in boys. Another notable investigation compared children with recurrent benign pain persisting for 1–2 years to children without recurrent pain (Perquin et al., 2003), finding that children differed not only in the characteristics of their initial pain reports, but also children with recurrent pain reported more emotional problems, and their mothers had poorer health than children without recurrent pain. Depressive symptoms were also associated with the generalization of pain from one site (e.g., neck pain) to widespread pain over a 1-year follow-up among school-age children (Mikkelsson, Sourander, Salminen, Kautiainen, & Piha, 1999). Only one prospective study has found that depressive symptoms did not predict future pain for children with idiopathic musculoskeletal pain (Flato, Aasland, Vandvik, & Forre, 1997). Notably, most prospective studies have found significant longitudinal relationships between depression/emotional problems and pain among children with idiopathic or benign pain.

Such findings in otherwise healthy children experiencing benign chronic pain suggest that depressive symptoms may also be a salient variable to examine in the context of children's disease-related pain. Therefore, the purpose of this study is to examine whether there are significant longitudinal associations between depressive symptoms and pain and/or functional disability among children with disease-related pain. If depressive symptoms were found to significantly predict pain and disability, depressive symptoms would then represent a modifiable, target of intervention. Although some investigators have suggested that psychological functioning in childhood chronic conditions should be examined noncategorically (Garstein, Short, Vannetta, & Noll, 1999), others advocate a disease-specific approach (Thompson, Gustafson, Gil, Godfrey, & Bennett Murphy, 1998) to

identify disease-specific constellations of factors that may be related to disease outcomes. Here, the same methodology and analytical model was used to examine the effects of depressive symptoms on disease-related pain and functional disability among children with either SCD or JIA. A disease-specific approach was chosen for two reasons. First, each group differed with regard to demographic characteristics that may influence pain and functional disability. Second, the etiology and presentation of pain symptoms and duration of disease is dissimilar for each group where pain in JIA is the result of an inflammatory process of the musculoskeletal system, the pain is usually mild to moderate intensity, and the disease can be diagnosed throughout childhood, while pain associated with SCD is because of vaso-occlusive events of the circulatory system, the pain is typically moderate to severe, and the disease is diagnosed at birth. By examining both groups over time, using the same methodology, we can assess the generalizability of the model across two chronic conditions for which chronic pain is a hallmark symptom. Finally, it is well established that caregiver and child report of pain and functional disability frequently differ (Ennett, DeVellis, & Earp, 1991; Palermo, Zebracki, Cox, Newman, & Singer, 2004). Therefore, both caregiver and child report of pain and functional disability were included in the analyses.

Given the robust cross-sectional relationships between depressive symptoms and pain and functional disability, we predicted significant longitudinal associations between depressive symptoms and pain and functional disability at study entry (T1), and child- and caregiver-reported pain intensity (PI) and functional disability for both disease groups at 6-months (T2) and 12–months (T3). Specifically, increased T1-depressive symptoms, higher levels of pain, and greater functional disability at T1 would be significantly associated with higher levels of pain and functional disability over the 1-year period (at both T2 and T3). Further, we tested whether the effect of T1-depressive symptoms on pain and disability at T2 and T3 was moderated by the level of pain and disability reported at T1. We based study hypotheses on the biopsychosocial model of pain, which posits that both psychological and physiological factors contribute to the variability in pain and disability outcomes (Turk & Flor, 1999). Thus, when pain and disability were at high levels (presumably because of the child's disease course), we hypothesized that psychological factors would account for less of the variance in subsequent pain experiences. Conversely, when pain and disability were at lower levels, we hypothesized that psychological symptoms would account for a greater proportion of the variability in subsequent pain. Therefore, we hypothesized that T1-depressive symptoms would have a greater effect on T2 and T3 pain and disability when T1 pain and disability was lower.

To test these hypotheses, general linear mixed modeling was used, a technique that affords several advantages for the analysis of longitudinal data sets. General linear mixed modeling allows the inclusion of covariates (such as age and gender), and data from all subjects to be included in the analyses, even those missing data at particular time points, provided data that are missing at random (Rubin, 1976). In this study, we controlled for child age, child gender, family income, and physician-rated disease severity. Finally, use of this analytical technique strengthens the conclusions that can be drawn about the temporal role of T1-depressive symptoms in predicting pain and disability over time.

Methods

Participants

Participants included 119 children and adolescents (63 with JIA and 56 with SCD), ages 8–17 years (M = 12.28 years, SD = 2.62 years). Children were recruited from outpatient hematology and rheumatology clinics at a large Midwest tertiary-care children's hospital. Children and their parents were eligible for the study, if they were (a) diagnosed with either JIA according to the Durban classification criteria (Petty et al., 1998) or SCD, (b) between the ages of 8–17 years, (c) not diagnosed with a developmental disability, and (d) literate in English. The disease groups significantly differed on the following demographic variables: gender, $\chi^2(1, N = 119) = 18.46$, $p < .001$; ethnicity, $\chi^2(2, N = 119) = 97.25$, $p < .001$; family income, $\chi^2(7, N = 119) = 41.73$, $p < .001$; and marital status, $\chi^2(1, N = 119) = 32.52$, $p = .001$.

Of the 127 children (66 with JIA and 61 with SCD) approached to participate in the study, 119 (93.7%) completed measures at two or more time points. Six participants withdrew because of time constraints, and two did not complete enough time points to be included in the analyses. No significant differences were observed between children who completed the study (at least 2/3 time points) and those who did not on basic demographic parameters (all ps > .05). Table I summarizes demographic and disease information for the sample of children with either SCD or JIA included in the analyses.

Procedures

Institutional review board approval to conduct the study was obtained from the hospital where subjects were

Table I. Descriptive Statistics for Time 1 Demographic and Disease Variables by Group

Variable	JIA ($n = 63$)	SCD ($n = 56$)
Caregiver age	40.40 (*SD* = 5.60)	36.88 (*SD* = 8.00)
Child age	12.44 (*SD* = 2.69)	12.14 (*SD* = 2.46)
Child gender*		
Male	12 (19%)	32 (57%)
Female	51 (81%)	24 (43%)
JIA disease subtypes		
Systemic	3 (4.8%)	–
Oligoarthritis	26 (41.3%)	–
Polyarticular negative	15 (23.8%)	–
Polyarticular positive	3 (4.8%)	–
Enthesitis	5 (7.9%)	–
Other	11 (17.5%)	–
SCD disease subtypes		
SS	–	47 (83.9%)
SC	–	5 (8.9%)
Beta + thalassemia	–	4 (7.1%)
Martial status*		
Married	42 (67%)	13 (23%)
Never married	4 (6%)	21(38%)
Divorced/separated	17 (27%)	22 (39%)
Ethnicity*		
Caucasian	55 (87%)	0 (0%)
African American	6 (10%)	56 (100%)
Other	2 (3%)	0 (0%)
Maternal education		
No high-school diploma	0 (0%)	5 (9%)
High school/general equivalency diploma	14 (22%)	17 (30%)
Vocational school/ some college	20 (32%)	16 (29%)
College graduate	20 (32%)	7 (12%)
Professional/graduate	7 (11%)	6 (11%)
Missing	2 (3%)	5 (9%)
Total income*		
<10,000–19,000	8 (13%)	27 (48%)
20,000–39,000	9 (14%)	15 (27%)
40,000–59,000	13 (21%)	7 (12.5%)
60,000 to >70,000	33 (52%)	7 (12.5%)
Physician-rated disease severity	2.58 (*SD* = 1.94)	3.92 (*SD* = 3.24)

JIA, juvenile idiopathic arthritis; SCD, sickle cell disease.
Physician-rated disease severity is averaged across all time points.
SC, hemoglobin SC disease.
SS, hemoglobin SS disease.
*$p < .01$.

recruited. Caregivers of potential participants were approached in the respective outpatient clinics (i.e., Sickle Cell Anemia Clinic or Rheumatology Clinic) by a trained research assistant between January, 2001, and August, 2002. Informed consent was obtained from all caregivers. At the time of study entry (T1), questionnaires were completed during the waiting time before and after outpatient subspecialty appointment visits. Participants completed their 6-month (T2) and 12-month (T3) follow-up at a subsequent clinic visit or via post. Several strategies were used to retain children over the course of the study. Subjects received compensation ($30 gift certificates) upon the completion of each wave of data collection. In addition, families were contacted by telephone at 1 month and by post at 3 months to promote continued participation and verify contact information. At 6 months, the data collection wave was started approximately 4–6 weeks before the due date until 4–6 weeks past the due date. Whether or not this data collection wave was completed, contact was made with families at 9 months to encourage study participation. Finally, the 12-month data collection was conducted using the same methodology as for the 6-month data collection. Following study entry, the children's medical charts were reviewed to obtain information concerning disease characteristics.

Measures

Demographic Questionnaire

At study entry, demographic information including child age, child gender, caregiver marital status, family income, caregiver education, and caregiver occupation was obtained via caregiver report.

Pain Intensity

Children and their caregivers independently rated the child's usual level of pain over the last few days at each time point. PI was measured using the validated Faces Pain Scale (Bieri, Reeve, Champion, Addicoat, & Ziegler, 1990), which contains a series of seven faces with anchors at the two ends representing 0, "no pain" to 6, "worst pain ever." This pain scale has been used in other samples of children with disease-related pain (e.g., Reid, Gilbert, & McGrath, 1998). Cross-informant relationships between caregiver and child report of PI ranged from .47 to .76 at each time point.

Functional Disability Inventory (Walker & Greene, 1991)

Children and their caregivers independently completed the Functional Disability Inventory (FDI) at each time point. The FDI describes the extent of restriction in performing 15 daily activities in the domains of school, home, recreation, and social interaction. Sample activities include walking to the bathroom, being at school all day, and doing homework. Respondents rated how difficult it was for the child to perform each activity in the past few days on a 5-point scale with response categories ranging from 0, "no trouble" to 4, "impossible" to perform

each activity. Scores range from 0 to 60 with higher scores indicating more disability. Acceptable internal consistency and test–retest reliability coefficients were reported by Walker and Greene (1991). Internal consistency for the current sample was α = .90 and .94 for caregiver and child report, respectively. Cross-informant relationships between caregiver and child report of functional disability ranged from .14 to .72 at each time point.

The Revised Child Anxiety and Depression Scale (Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000)

The Revised Child Anxiety and Depression Scale (RCADS) is a 47-item instrument designed to assess children's self-report of depression and anxiety corresponding to several Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) disorders, including major depression and anxiety disorders. Children completed this measure at T1 only. Each item involves rating symptom frequency on a 4-point scale from "never" to "always." Items are scored 0–3, with higher scores indicating greater frequency. *T* scores are calculated based on child gender and grade in school. The major depressive disorder (MDD) subscale was used in the data analyses to characterize child-depressive symptoms. Adequate internal consistency (α = .76 for MDD scale) has been demonstrated. Test–retest reliability over 1-week was adequate, and validity has been demonstrated through relationships with other depression and anxiety measures (Chorpita et al., 2000). In receiver–operator characteristic analyses, a cutoff score on the MDD subscale of 11 optimized sensitivity and specificity for the prediction of MDD in a clinical sample (Chorpita, Moffitt, & Gray, 2005). Internal consistency for this sample was moderate (αs = .79 for both groups).

Provider Assessment Form

The subspecialty physician for each child completed a disease-specific provider assessment form that included disease classification, details of treatments including medication regimens as well as ratings of their perception of the child's disease severity. Disease severity was assessed via a 10-cm visual analogue scale with anchors at the two ends representing "not severe at all" to "extremely severe." Similar assessments of physician perception of disease severity have been used in previous research with children with chronic health conditions (e.g., Ravelli et al., 1997). Physicians were blind to participant rated levels of pain and functional disability.

Analysis Plan

First, descriptive statistics were calculated for each group (Table II). Then general linear mixed modeling was used to examine predictors of child- and caregiver-reported PI and FDI of the child. In the general linear mixed-modeling approach, models for means and variance–covariance parameters are fit to repeated measures. Specifically, an outcome (i.e., PI and FDI) is predicted from fixed components, random components, and error. Estimates are the fixed-effect parameters that describe the population mean behavior. Such an approach is akin to a repeated measures analysis of covariance but allows data from all subjects to be included in the analyses, even those missing data at particular time points, provided data are missing at random (Rubin, 1976). The analyses were conducted using SAS/STAT® Software (Version 9.1) Proc Mixed. Maximum likelihood (ML) estimation methods with Satterthwaite approximations were used to compute degrees of freedom employed on each general linear mixed model (Littell,

Table II. Means (Standard Deviations) and Ranges for Independent and Dependent Variables in Children with Sickle Cell Disease (SCD) or Juvenile Idiopathic Arthritis (JIA) at Times 1, 2, and 3

	JIA			SCD		
Variable	T1 (n = 63)	T2 (n = 45)	T3 (n = 55)	T1 (n = 56)	T2 (n = 36)	T3 (n = 41)
Caregiver report						
PI	2.37 (1.52)	1.80 (1.24)	1.83 (1.33)	3.43 (1.99)	2.70 (2.11)	2.78 (1.84)
Range	0–6	0–5	0–5	0–6	0–6	0–6
FDI	9.47 (11.83)	5.55 (7.19)	6.46 (9.21)	13.07 (13.85)	15.48 (14.82)	11.01 (13.93)
Range	0–46	0–32	0–39	0–49	0–48	0–55
Child report						
PI	2.35 (1.72)	2.10 (1.51)	1.84 (1.42)	3.45 (1.94)	2.70 (2.00)	2.65 (1.75)
Range	0–6	0–5	0–5	0–6	0–6	0–6
FDI	10.16 (9.35)	6.07 (6.45)	6.95 (8.21)	10.99 (10.67)	12.87 (13.73)	10.69 (11.07)
Range	0–39	0–23	0–35	0–35	0–48	0–41
MDD	45.34 (11.48)	–	–	49.07 (12.43)	–	–
Range	30–86	–	–	30–75	–	–

FDI, Functional Disability Inventory; MDD, *T* score on major depression disorder subscale of the Revised Child Anxiety and Depression Scale; PI, pain intensity.

Milliken, Stroup, & Wolfinger, 1996). The covariance structure was modeled by either using an arbitrary unstructured matrix or a compound symmetry structure, which assumed equal variances across time and a common correlation between all pairs of time points. The covariance model fitting best according to the Akaike Information Criterion (AIC) was chosen (Akaike, 1974).

Here, the effects of the predictors (T1-depressive symptoms and T1 PI/FDI) were estimated for each dependent variable (PI and FDI) for both child- and caregiver-report at T2 and T3. Time (T2 and T3) was included in the model as a fixed effect. Caregiver and child-report FDI were log transformed because of a positively skewed distribution of scores. Child age, child gender, family income, and physician-rated disease severity were chosen as covariates based on previous research demonstrating a consistent and significant relationship with either the predictor or the outcome variables (El-Metwally et al., 2004; Thompson & Gustafson, 1996). The number of covariates was intentionally limited in these analyses because of considerations of power and overfitting the models. Three-way interactions were examined first to rule out the possibility of a T1-depressive symptoms × time × T1 PI/FDI interaction for each of the hypothesized models. There was a lack of three-way interactions for any of the models. Two-way interactions (time × T1 PI/FDI, T1-depressive symptoms × T1 PI/FDI, and T1 depressive symptoms × time) were then examined. If no significant two-way interaction was observed in the model, then the most basic model was run with no interactions and depressive symptoms, and T1 PI/FDI were examined as main effects. A significant main effect for depressive symptoms was interpreted as supportive of our hypothesis that T1-depressive symptoms would predict PI and FDI at T2 and T3. Analyses were conducted separately for each disease group.

Results

Descriptive Data on PI, Functional Disability, and Depressive Symptoms

Frequency data were calculated for demographic and disease characteristics (Table I). In children with SCD, weekly pain was reported in 47.4% (T1), 17.1% (T2), and 28.2% (T3) of the sample. In children with JIA, weekly pain was reported in 63.4% (T1), 50.0% (T2), and 37.9% (T3) of the sample. Descriptive statistics (means and standard deviations) were calculated for each disease group on the dependent variables (Table II). Fifty percent of children with SCD and 50% of children with JIA reported at least mild to moderate PI during the study. Similarly, approximately 42% of children with SCD (range = 0–35) and 39% (range = 0–39) of children with JIA reported an FDI score of 10 or above, which is considered the moderate to high range of disability (Kashikar-Zuck et al., 2001). Most of the children with JIA and SCD reported depressive symptoms in the average range (*T*-score range = 30–65). Approximately 14% of children in the JIA group and 27% of children in the SCD group reported a raw score equal to or above 11 on the MDD subscale, which is considered the cutoff score for the prediction of MDD (Chorpita et al., 2005).

Primary Analyses for the JIA Group

Caregiver Report

First, we examined whether T1-depressive symptoms predicted caregiver-reported PI. There was a lack of significant two-way interactions for PI. However, a significant main effect was found for T1 PI, $t(42.5) = 2.41$, $p = .02$. In addition, disease severity, $t(40.2) = 2.89$, $p = .006$, and income, $t(43.5) = -3.18$, $p = .003$, were significant covariates. Specifically, caregivers of children with JIA with greater physician-rated disease severity, from lower income homes, and greater PI at the initial assessment, reported significantly higher PI for their child at both T2 and T3. Owing to the lack of significant two-way interactions for caregiver FDI, main effects were examined. One main effect, caregiver T1 FDI predicted FDI at T2 and T3, $t(52.5) = 5.45$, $p < .001$, for children with JIA. There were no significant covariates for caregiver-reported FDI scores. Table III summarizes these findings.

Child Report

The relationship between T1-depressive symptoms and child-reported pain parameters were then examined in the JIA group.[1] Consistent with hypotheses, a significant depressive symptoms by T1 PI interaction was observed for PI, $t(43) = -2.93$, $p = .005$. Specifically, the effect of depressive symptoms on PI at T2 and T3 was moderated by the level of PI at T1, where depressive symptoms had a greater effect on future PI when T1 PI was lower. Estimates of depressive symptoms were calculated at the 10th, 25th, 50th, 75th, and 90th percentiles of T1 PI (T1 PI = 0, 1, 2, 3, and 5, respectively) to quantify the degree

[1]Regression analyses were conducted examining depressive symptoms as a predictor of change in PI/FDI from T1 to T3 for both groups. Only significant results are reported here. For children with JIA, depressive symptoms significantly predicted the difference in self-reported FDI from T1 to T3 after controlling for demographic and disease parameters ($R^2_{change} = .16$, $p = .004$). Results of the regression analyses for children with JIA are commensurate with the primary analyses using mixed modeling.

Table III. Predictors of Caregiver-Rated Child Functional and Pain Outcomes

	JIA			SCD		
Variable	β	*SE*	*p*	β	*SE*	*p*
FDI						
Age	.063	.042	.135	.001	.001	.529
Gender	.033	.275	.906	.379	.358	.296
Severity	.039	.059	.512	.059	.054	.276
Income	–.091	.051	.080	–.195	.081	.021
MDD	.002	.010	.855	–.014	.014	.371
Time	.129	.145	.378	.313	.215	.158
T1 FDI	.506	.093	<.001	.211	.156	.183
PI						
Age	–.015	.048	.754	–.002	.001	.155
Gender	.077	.324	.814	–.875	.412	.040
Severity	.199	.069	.006	–.082	.006	.188
Income	–.179	.056	.003	–.177	.093	.064
MDD	.010	.011	.382	.107	.039	.008
Time	–.098	.177	.581	–.232	.255	.370
T1 PI	.208	.086	.020	1.50	.419	.001
MDD × T1 PI	–	–	–	–.026	.009	.007

FDI, Functional Disability Inventory; JIA, juvenile idiopathic arthritis; MDD, *T* score on major depression disorder subscale of the Revised Child Anxiety and Depression Scale; PI, pain intensity; SCD, sickle cell disease.

to which depressive symptoms predicted T2/T3 PI based on the level of T1 PI. As illustrated in Fig. 1, depressive symptoms were significantly associated with T2/T3 PI at the 10th (T1 PI = 0: β = .0691, p = .003), 25th (T1 PI = 1: β = .0518, p = .006), and 50th (T1 PI = 2: β = .0345, p = .023), but not at the 75th (T1 PI = 3: β = .017, p = .213) and 90th (T1 PI = 5: β = .018, p = .340) percentiles of T1 PI. Also consistent with study hypotheses, T1 FDI moderated the relationship between depressive symptoms and T2/T3 FDI where lower the T1 FDI the greater the

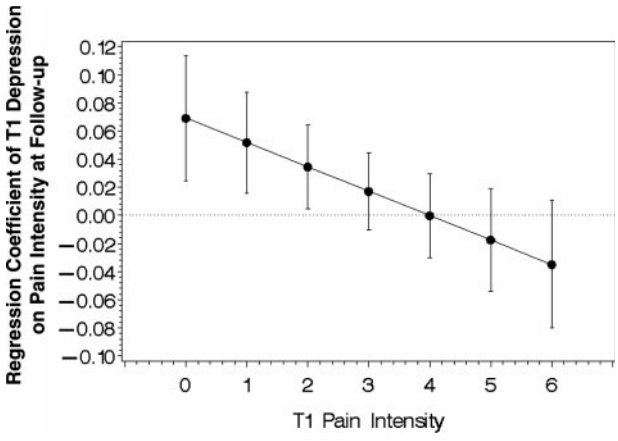

Figure 1. Estimated regression coefficient of depressive symptoms [estimate ± 95% confidence interval (CI)] on child-reported pain intensity (PI) at follow-up in the JIA group, plotted against T1 raw scores of PI. The 10th, 25th, 50th, 75th, and 90th percentiles of T1 PI are equivalent to the raw scores of 0, 1, 2, 3, and 5, respectively.

Table IV. Predictors of Self-Reported Child Functional and Pain Outcomes

	JIA			SCD		
Variable	β	*SE*	*p*	β	*SE*	*p*
FDI						
Age	.031	.043	.480	.000	.001	.972
Gender	.322	.297	.284	–.081	.244	.742
Severity	–.070	.064	.277	–.016	.037	.666
Income	–.060	.052	.250	–.249	.055	.000
MDD	.065	.027	.021	.010	.012	.448
Time	.003	.145	.980	.229	.225	.319
T1 FDI	1.59	.413	.000	.263	.132	.058
MDD × T1 FDI	–.026	.009	.009	–	–	–
PI						
Age	.048	.056	.378	.001	.001	.202
Gender	.047	.378	.900	–311	.415	.459
Severity	.056	.080	.490	–.053	.063	.396
Income	–.004	.067	.948	–.232	.093	.016
MDD	.069	.022	.003	.019	.017	.275
Time	.291	.244	.240	–.166	.279	.558
T1 PI	1.08	.302	.001	.314	.106	.006
MDD × T1 PI	–.017	.006	.005	–	–	–

FDI, Functional Disability Inventory; JIA, juvenile idiopathic arthritis; MDD, *T* score on major depression disorder subscale of the Revised Child Anxiety and Depression Scale; PI, pain intensity; SCD, sickle cell disease.

influence of T1-depressive symptoms on future reports of functional disability, $t(48.3) = -2.72$, p = .009. Estimates of depressive symptoms were calculated at the 10th, 25th, 50th, 75th, and 90th percentiles of T1 FDI to quantify the degree to which depressive symptoms predicted T2/T3 FDI based on the level of T1 FDI. Depressive symptoms were significantly associated with T2/T3 FDI at the 10th, ln(T1 FDI) = 0: β = .0645, p = .021; 25th, ln(T1 FDI) = 1.1: β = .036, p = .05; but not at the 50th, ln(T1 FDI) = 2.08: β = .011, p = .392; 75th ln(T1 FDI) = 2.89: β = –.009, p = .464; and 90th, ln(T1 FDI) = 3.18: β = –.017, p = .223, percentiles of T1 FDI. There were no significant covariates observed. Please see Table IV for a summary of these findings.

Primary Analyses for the SCD Group

Caregiver Report

A different pattern of findings were observed for caregivers of children with SCD.[2] A significant depressive

[2]For children with SCD, depressive symptoms significantly predicted the difference in caregiver-reported FDI from T1 to T3 after controlling for demographic and disease parameters, (R^2_{change} = .20, p = .009). The results of the regression analyses for children with SCD are slightly different where with mixed-modeling depressive symptoms were not a significant predictor; however, this difference is likely because of the use of T3 only (and not T2 and T3) means.

symptoms × T1 PI interaction, $t(36.5) = -2.87$, $p = .007$, predicted PI regardless of time. Specifically, the lower the level of caregiver-reported PI the greater the effect that depression has on PI at T2 and T3. Estimates of depressive symptoms were significantly associated with T2/T3 PI at the 10th (T1 PI = 0: $\beta = .107$, $p = .008$) and 25th (T1 PI = 2: $\beta = .023$, $p = .023$), but not at the 50th (T1 PI = 3: $\beta = .030$, $p = .111$), 75th (T1 PI = 5: $\beta = -.022$, $p = .270$), and 90th (T1 PI = 6: $\beta = -.048$, $p = .069$) percentiles of T1 PI. Finally, child gender was a significant covariate, $t(36.2) = -2.12$, $p = .04$, for this model where girls reported significantly greater PI than boys. There was a lack of significant two-way interactions or main effects for the prediction of FDI scores. One significant covariate was observed. Family income, $t(41.6) = -2.40$, $p = .021$, predicted FDI at T2 and T3, indicating that lower income was associated with greater functional disability. Table III summarizes these findings.

Child Report

There was a lack of two-way interactions for predicting child-reported PI among children with SCD. However, one main effect, T1 PI, $t(36.3) = 2.96$, $p = .006$, predicted PI at T2 and T3. Family income, $t(40.7) = -2.50$, $p = .016$, was a significant covariate in the final PI model. There was a lack of two-way interactions or main effects for the prediction of FDI scores. However one covariate, family income, predicted subsequent functional disability, $t(30.8) = -4.50$, $p < .001$. Inconsistent with the study hypothesis, depressive symptoms did not significantly predict child-reported PI or functional disability for children with SCD. Table IV summarizes these findings.

Discussion

To our knowledge, this is the first longitudinal study to examine the effects of depressive symptoms on caregiver- and child-reports of PI and functional disability over time among children with disease-related pain. These findings reveal complex interrelationships between disease and psychological factors associated with pain and disability outcomes. Specifically, for children with JIA, depressive symptoms predicted PI 6 and 12 months later only when the initial self-report of PI was in the mild to moderate range. The same relationships held for functional disability among children with JIA, where depressive symptoms were associated with future disability only when initial self-reports of disability were relatively low. Similarly, for the SCD group, depressive symptoms were associated with future caregiver-reported PI in the context of less intense initial pain. However, child-reported PI and disability and caregiver-reported disability were not associated with initial reports of depressive symptoms among children with SCD. Thus, our hypothesis that depressive symptoms would function as a risk factor for subsequent disease-related pain and functional disability across these disease groups was partially supported.

Our findings are consistent with previous longitudinal studies in cohorts of children with recurrent benign pain, where both pain characteristics and psychological symptoms were predictive of future pain (Perquin et al., 2003). Yet, this study is unique in that it unveiled complex interrelationships between pain/disability and depressive symptoms by examining the interactions of initial pain/disability ratings and depressive symptoms. These findings suggest that the degree to which depressive symptoms are associated with pain and disability will depend partly upon the individual's history of pain and disability.

An unexpected finding was the consistency with which income was associated with PI and functional disability for both caregiver and child reports in the SCD group but not in the JIA group. Over time, children with SCD from lower income homes experienced more intense pain and functional disability according to both caregiver and child report. The reason for these stark-group differences with regard to income is unclear and requires further investigation into potential ethnic, societal, neighborhood, family, and individual processes that may link lower income with pain and disability (Chen, Matthews, & Boyce, 2002). It is possible that this finding is attributable to differences in perceptions or reporting of pain between ethnic groups. However, alternative explanations are also plausible. Previous literature examining the relationship between socioeconomic status and health outcomes among children has identified many potential mediators, such as inconsistent family relationships, child-care quality, social support, access to health care, and cognitive processes (Chen et al., 2002). Examination of such variables has yet to be conducted among children with SCD. Our findings strongly argue for such an investigation into moderators/mediators of the income–pain and income–disability relationships among children with SCD.

Importantly, the natural course of pain and disability in children with disease-related pain has not been clearly elucidated, nor do we know the impact of specific medical and psychological treatments on long-term functional outcomes or quality of life in these children. For example, to evaluate the effects of psychological treatment over time on pain and disability, investigators will

need to consider whether pain outcomes are expected to increase, decrease, or to remain stable. In this study, mean PI and functional disability scores decreased over time. This improvement may be attributable to specific changes in disease processes, to the development of new coping skills with maturation, or to measurement effects. However, in this study design, we were unable to identify the specific reason for improvement in pain and disability over the course of the year. Additional studies are needed to clarify the natural course of pain and disability in children with chronic disease-related pain.

The relationship between depressive symptoms and caregiver-reported perceptions of the child's pain were not consistent with the child-reported outcomes. This difference is similar to previous studies in which child- and caregiver-report of pain and functional disability are discrepant (e.g., Ennett et al., 1991). Alternatively, this finding may be an artifact of higher covariance between self-reports of depressive symptoms, and self-reported outcome measures increasing the likelihood of finding a significant relationship. Regardless of the source of this observed discrepancy between child and caregiver pain reports, these differences highlight that caregiver and child reports of pain are not interchangeable and that using multiple informants provides unique information when assessing pain in children. In the future, investigators will need to explicitly consider factors related to inter-informant differences in reports of pain and disability. There is preliminary evidence in a sample of children with JIA suggesting that such disagreements in reporting of pain and functional disability by caregivers and their children with JIA are associated with underlying depressive symptoms in children (Palermo et al., 2004).

These findings must be considered in light of several limitations. First, the participants were not newly diagnosed. Thus, the changes over time examined here are not necessarily at the same point in the disease course for all of the patients included in the study. Second, depressive symptoms were only evaluated at study entry. Therefore, it cannot be determined how levels of depressive symptoms (which fell in the low to moderate range) changed over the year in relationship to changes in pain and disability. For example, we do not know whether depressive symptoms improved in parallel with improvements in pain and disability. Third, this study had limited measures of disease activity and treatments received by children, and thus the specific course of disease and prognosis over time for children with JIA- and SCD-related pain is unclear. Fourth, sending follow-up measures via post to some participants decreased the degree of control over the conditions in which the forms were completed and the level of assistance children may have had from parents in completing their measures. Therefore, the influence of these conditions on the study outcomes are unknown. Finally, the study was not able to test mediators of the relationship between depressive symptoms and pain and functional disability. Previous studies suggest that individual coping (Gil et al., 1997) and family factors (Peterson & Palermo, 2004) may be related to pain and disability and are potentially amenable to behavioral intervention.

This study raises critical questions for future investigation. For instance, what level of depressive symptoms puts children with chronic diseases "at risk" for experiencing more chronic problems with pain and functional disability? A small subgroup of children in this sample scored above the cutoff for predicting major depression (Chorpita et al., 2005). However, this does not answer the critical question, what level of depressive symptoms, under what conditions influence current and longitudinal associations with pain? Further research specifying how levels of depressive symptoms are associated with increased pain and disability through methods such as Receiver Operating Characteristic analyses and other techniques are necessary to facilitate the identification of children at risk for increased disease-related pain in clinical settings. In addition, other types of psychological symptomatology, such as anxiety and their relationship to pain and disability, should be examined. Future research should examine specific types of depressive symptoms (e.g., hopelessness) as well as cognitive appraisals related to depression (e.g., catastrophizing) to provide further support for the types of behavioral interventions that may be useful for reducing emotional distress in these patients.

Many clinical implications can be drawn from these findings. A multifactorial assessment of pain symptoms, history of pain and disability, family socioeconomic status, and past and current depressive symptoms may be useful in the optimal management of children with disease-related pain. For example, all children with SCD and JIA who are experiencing disease-related pain might benefit from general screening of depressive symptoms and pain history to identify children that may benefit from behavioral intervention to reduce emotional distress, improve the child's ability to cope with pain, and enhance daily functioning. For children with SCD who are from lower income homes, it may be particularly important to assess how family resources influence pain/disability such as identifying barriers of effective management (Mitchell et al., 2004) and offering resources as

well as behavioral interventions to reduce child pain and functional impairment. Furthermore, it will be important to determine whether the treatment of depressive symptoms and potential mediators (such as cognitive appraisals) lead to improved pain and functional outcomes of children with chronic conditions (Clingempeel & Henggeler, 2002).

Acknowledgments

This study was supported by NIMH Grant K23 MH01837 (TMP). We thank Brian Berman, MD, Helen Gutin, RN, Arthur Newman, MD, Nora Singer, MD, Samantha Cox, and Duaré Valenzuela for their contributions to the project. We are grateful to the children and families who participated in this study

Received July 14, 2004; revisions received December 22, 2004 and April 26, 2005; accepted May 5, 2005

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