Profiling Behavioral and Psychological Symptoms in Children undergoing treatment for Spondyloarthritis and Polyarthritis

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ABSTRACT:

Objective: Few studies examine psychopathology in different juvenile idiopathic arthritis (JIA) subtypes and disease activity states. We aimed to 1) Evaluate emotional and behavioral symptoms in children with spondyloarthritis (SpA) and polyarticular arthritis (PolyA) as compared to a national normative population using the Child Behavior Checklist (CBCL), and 2) Evaluate the relationship between CBCL scores and disease activity.

Methods: JIA patients aged 6-17 years with SpA or PolyA were recruited from our Pediatric Rheumatology clinic from April 2018 to April 2019 and the CBCL and Juvenile Arthritis Disease Activity Score (cJADAS10) were completed. Primary outcome measures were CBCL total competence, internalizing, externalizing and total problems raw scores. We compared outcomes from each group to national CBCL normative data. To investigate the relationship between CBCL scores and disease activity, we ran a generalized linear regression model for all arthritis patients with cJADAS10 as the main predictor.

Results: There were 111 patients and 1753 healthy controls. Compared to healthy controls, SpA or PolyA patients had worse total competence and internalizing scores. Higher cJADAS10 scores were associated with worse total competence, worse internalizing, and higher total problems scores. Most of these differences reached statistical significance ($p<0.01$). Self-harm/suicidality was almost four-fold higher in patients with PolyA than healthy controls (OR 3.6, 95% CI 1.3-9.6, $p=0.011$).

Conclusion: Our study shows that SpA and PolyA patients with more active disease have worse psychological functioning in activities, school and social arenas and more internalized emotional disturbances suggesting the need for regular mental health screening by rheumatologists.

Introduction:

There is mounting evidence regarding the significant overlap between rheumatologic and mental health impairments. (1)(2) However, this relationship is currently understudied in the pediatric population, including those with juvenile idiopathic arthritis (JIA), the most common chronic rheumatic disease in children, affecting 1-4 per 1000. (3) Patients with JIA have been found to have an increased risk of behavioral and mental health disorders, but research has not yet clarified the relationship between psychopathology and arthritis disease activity, nor have studies distinguished between JIA subtypes, which have different underlying mechanisms and perhaps variable risk for psychological symptoms. (4)(5)(6)(7)(8)

The overlap between rheumatologic and psychiatric disorders may be caused by both physiological and psychological factors, but the contribution of each is unknown and difficult to study. Regardless of the cause of the mental health problems, standard evidence-based approaches to identify and treat mental health impairments are important to pursue. Therefore, it is important for the rheumatology field to better understand psychological/psychiatric profiles in rheumatologic conditions to better equip clinicians with awareness and tools to properly screen patients.

Adults with psoriatic arthritis and ankylosing spondylitis have been found to have increased rates of obsessive-compulsive symptoms, anger-hostility, paranoid ideation, somatization, anxiety, depression, and self-harm. (9)(10)(11)(12)(13)(14) While rheumatoid arthritis (RA) patients with depression have poorer RA outcomes (i.e., worse mortality, more comorbidities and higher pain levels). (15)

Patients with juvenile SpA and polyarthritis have worse self-reported pain, physical functioning, remission rates and quality of life, putting them at high risk for psychopathology. (3)(16)(17)(18)(19) The relationship between these two JIA subtypes and mental health have not been specifically explored. While pediatric patients with SpA and PolyA have been included

in some studies, the number of subjects has been low. (4)(7) To address the research gap, this study evaluates behavioral and emotional symptoms in children with SpA and polyarticular arthritis (PolyA) separately and compares them to a national normative population using the Child Behavior Checklist (CBCL).

The purpose of this study was two-fold: 1) To report the emotional and behavioral profile in two common forms of chronic arthritis in children; juvenile spondyloarthritis (SpA) and polyarthritis (PolyA) as compared to a national normative population using the CBCL, and 2) To evaluate the relationship between CBCL scores and disease activity using the cJADAS10.

Methods:

Study design, setting and participants

In this cross-sectional study, patients with JIA between ages of 6 -17 were recruited from our pediatric rheumatology clinic from April 1st, 2018 to March 31st, 2019. Pediatric rheumatologists determined the diagnosis by history, physical examination, labs, and/or radiographic findings. Patients included in the SpA group include: 1) Patients meeting the International League of Associations for Rheumatology (ILAR) criteria of enthesitis-related arthritis, undifferentiated arthritis, or psoriatic arthritis; 2) inflammatory bowel disease (IBD)-related arthritis; 3) the Berlin criteria for reactive arthritis. Patients in the PolyA group included those meeting ILAR criteria for polyarticular JIA or extended oligoarticular JIA. We excluded patients with active IBD, severe psoriasis (involvement of body surface area > 10%), and severe developmental delay as determined by the provider as these features may affect their mental health beyond the arthritis and musculoskeletal conditions we examined. We did not exclude patients with mild to moderate developmental delays, or subjects who carried a diagnosis of a mental health disorder as the patients' mental health was our topic of investigation. The

Stanford Institutional Review Board approved the study protocol (#42307). Consents from parents and assents from children were obtained.

The national normative population (n=1,753) data provided by the Achenbach System of Empirically Based Assessment (ASEBA) came from the representative samples of 2,029 American children from the National Survey of Children, Youths and Adults. The CBCL was completed for survey participants by parents and/or guardians per the guidelines of ASEBA. (20)

Data sources and study measures

After study consent, parents completed the paper form of the CBCL for their children at the clinic or right after the clinic visit. (20) This was self-administered although clinicians were available for questions. The internalizing problems score is derived from the sum of the following syndrome scores: anxious/depressed, withdrawn/depressed, and somatic complaints scores. The externalizing problems score combines the rule-breaking and aggressive behavior syndrome scores. The total problems score is the sum of scores from 113 items rated by parents based on the following response options: “not true”, “somewhat or sometimes true”, and “very true or often true”, that best describe the patient now or within the past six months.

The primary outcome measures include total competence score, internalizing problems score, externalizing problems score, and total problems score. Exploratory analyses (identified *a priori*) include OCD problem score, self-harm, and individual syndrome scores under internalizing problems and externalizing problems scores. Self-harm is a binary variable derived from question 18 (deliberately harms self or attempts suicide) and question 91 (talks about killing self) of the CBCL.

For disease activity, both clinicians and parents contributed to the clinical 10-joint Juvenile Arthritis Disease Activity Score (cJADAS10, range 0-30), which is a validated composite score specific to JIA and measuring three domains: active joint count and a 10 cm

visual analog scale to measure parent and physician global assessment of the child's well-being. (21) We also reviewed charts to collect demographic and clinical information and identify the presence of HLA-B27, arthritis medications, and psychiatric, developmental, and medical comorbidities. Medical comorbidities were defined as any current medical diseases through chart reviews and the CBCL questionnaire.

Statistical analysis

Demographic and clinical characteristics of patients with SpA and PolyA were examined by summary statistics. Per the ASEBA CBCL manual, T scores between 65 - 69 (93-97th percentiles) are considered to be in the "borderline clinical range" while T scores ≥ 70 (>97th percentiles) are considered to be the "clinical range". Scores in the borderline and clinical ranges significantly discriminate between children who are referred for emotional health or special education services for behavioral/emotional problems and those who are not referred.

Using generalized linear regression models and controlling for age and sex, outcome measures between patients from each group (SpA/PolyA) and controls were compared, and the relationship between primary outcome measures and disease activity (cJADAS10) were examined with cJADAS10 as the main predictor. Raw scores were used for comparisons to account for the full-range variations. For exploratory analyses, the same models were employed to examine the secondary outcome measures (OCD scores and syndrome scores) and a logistic regression model was performed for self-harm.

All statistical tests were two-sided, and they were considered statistically significant if $p < 0.013$ (which is 0.05 divided by 4) for the primary outcome measures to account for the multiple testing, and $p < 0.05$ for the exploratory analyses. Data were analyzed with the Statistical Analysis Systems software program (SAS® University Edition, Cary, North Carolina, the United States).

Results:

Our study sample was comprised of 111 patients: 53 with SpA and 58 with PolyA. In both groups, the median age at CBCL completion was 13-14 years, and more than half of patients were female (see Table 1). The majority of SpA patients carried a diagnosis of enthesitis-related arthritis (n=26), psoriatic arthritis (n=14) and undifferentiated arthritis (n=6). More than 80% of patients were taking medications for arthritis at the time of administering the CBCL. More than half of the patients in each arthritis group were on aggressive medical therapy (i.e., a biologic or combination of a disease-modifying antirheumatic drug (DMARD) and biologic). In the SpA group, more patients had medical comorbidities than those with PolyA.

Using the percentile cut-off of 93%, the proportions of patients having abnormal range scores (defined by ASEBA as borderline or clinical range) in total competence, internalizing problems, externalizing problems, and total problems were 4%, 11%, 0%, 4%, in SpA, and 2%, 16%, 3%, 7%) in PolyA, respectively. Approximately 4-5% of healthy controls had these scores within the abnormal ranges.

On generalized linear regression, the age and sex-adjusted score differences between healthy controls and patients with SpA or PolyA were small (see Table 2). Both the SpA and PolyA groups had lower total competence and higher internalizing problems scores (mainly driven by somatic complaints which includes headaches, nausea, vomiting, stomachache, etc.). This was only statistically significant for patients with PolyA. Both arthritis groups had lower externalizing problems scores than healthy controls, indicating fewer reported problems with aggressive, hyperactive, noncompliant, and under-controlled behaviors. Both arthritis groups were similar to the control groups with regards to the total problems score.

Patients' parents (five in the PolyA group and one in the SpA group) endorsed the symptoms: "talks about killing self" (n=4), "deliberately harms self or attempts suicide" (n=3), on the CBCL. These patients were not statistically different than the rest of the cohort regarding use of biologics, disease duration or cJADAS10. Endorsement of self-harm behaviors/suicidality

was significantly higher in the PolyA group than the normative population. (OR 3.6, 95% CI 1.3-9.6, $p=0.011$).

Higher disease activity, as reflected by higher cJADAS10, was associated with lower total competence and higher internalizing problems and total problems scores (see Table 3). The externalizing problems scores (including rule-breaking and aggressive behaviors), however, were unaffected by disease activity.

Figure 1 shows the scatter plots of composite CBCL T scores against cJADAS10 in patients with SpA and PolyA. Most of our arthritis patients had a cJADAS10 less than 8. Total competence T scores correlated inversely with the cJADAS10 in both groups. Internalizing problems, externalizing problems, and total problems T scores correlated positively with cJADAS10 in both groups. Although, in the polyarthritis group, there was an inverse correlation when cJADAS10 was above 7.5.

We performed a sensitivity analysis by excluding 20 arthritis patients with ADHD, autism, depression, anxiety, avoidant restrictive food intake disorder, and OCD. The directions of change were consistent with the primary analysis, but the only analyses which were statistically significant were the externalizing problems scores which were less when compared to the normal controls (see Appendix Table 1).

Discussion:

Our study evaluated behavioral symptoms in SpA and PolyA patients using the CBCL. The CBCL is one of the most widely validated instruments for evaluation of emotional and behavioral symptoms in children and has been used in thousands of studies. (22) It generates eight syndrome scores: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. It then summarizes these syndrome scores into composite scores to estimate the

child's total competence score (functional performance), internalizing problems score, externalizing problems score and total problems score. (20)(23)

We found that a higher proportion of our SpA and PolyA patients (11% and 16%, respectively) had borderline or clinical range of abnormalities in internalizing symptoms when compared to healthy controls (5%). However, on generalized linear regression, the age and sex-adjusted score differences between patients and controls were small. When compared with healthy controls, arthritis patients had lower total competence (i.e., functional psychological impairments) and higher internalizing problems scores (anxious/depressed, withdrawn/depressed, somatic complaints). Importantly, higher disease activity was associated with lower total competence and higher internalizing and total problems scores. These findings underscore the importance for clinicians to screen children with arthritis for social, school and activity competencies and internalized emotional disturbances, especially during periods of higher disease activity.

Our findings are consistent with existing literature that children with JIA are at risk for internalizing symptoms and functional impairment. (7)(24)(25)(26) Internalizing scores in both SpA and PolyA patients were mainly driven by somatic symptoms (and not by anxiety, depression, or social withdrawal). Somatic symptoms (e.g., headaches, nausea, vomiting, stomachache, etc.) can be contributed by both arthritis and the side effects of medication as was found in a study by Noll et al. (27) In our study, when we controlled for disease activity, the internalizing problems score was no longer being driven by somatic complaints but rather driven by anxious/depressed and withdrawn/depressed scores.

The absolute CBCL score differences between our study patients and healthy controls were small after controlling for age, gender, and medical comorbidities. It is important to note that the majority of these JIA patients were on aggressive immunomodulatory therapies and had low cJADAS10 scores indicating minimal disease activity. This finding coupled with the finding that psychopathology is worse with higher arthritis activity may be another justification for

treating juvenile arthritis aggressively beyond the goal of joint and physical function preservation.

Interestingly, we saw a plateau and even improvement of CBCL scores in PolyA patients with a cJADAS10 > 7.5 (Figure 1). This finding of inversely correlating scores (when cJADAS10 rose above 7.5) in patients with PolyA may deserve further exploration since one might speculate that those patients with higher cJADAS10 had either a different treatment path or different immunogenetic profile that somehow correlates to better CBCL scores. Importantly, this finding needs to be interpreted with caution since there were few patients with PolyA and cJADAS10 greater than 7.5.

Not surprisingly, existing evidence regarding the relationship between psychiatric symptoms and arthritis disease activity varies likely reflecting the heterogeneity of these arthritis cohorts with regards to arthritis subtype, treatment status, and study design. (4)(5)(6)(7) In one study of patients with JIA, psychiatric symptoms correlated more with physical disability than the physician-rated disease activity score or the number of active joints on physical examination. (5) Another group of researchers found that in adolescents with newly diagnosed JIA, depression was associated with active disease, pain, and disability; but after one year, depression remained associated with pain and disability, but not disease activity. (6) While our study shows an association between disease activity and psychiatric symptoms and functioning, we did not assess physical disability formally nor did we study physician-rated disease as a separate variable but rather used the cJADAS10 which is a composite index that incorporates the physician assessment with a parent/patient assessment, and an active joint count. When looking further at the relationship between disease severity and mental health in our exploratory analyses, we found that higher cJADAS10 was associated with increased anxious/depressed and withdrawn/depressed scores (syndrome scores within the internalizing problems score), but not with somatic complaints (Table 3).

Medical comorbidities, such as celiac disease, inflammatory bowel disease, uveitis, cataracts, chronic renal disease, Raynaud disease, psoriasis, migraines, asthma, etc. were common in our patients (60% in SpA patients and 43% in PolyA patients). Surprisingly, a comorbid pain syndrome such as fibromyalgia was uncommon in our cohort (<1% of patients). Although it is not possible to fully know the impact of these disorders on mental health in our cohort, we did control for medical comorbidities in our multivariate analysis. We also did a sensitivity analysis whereby we excluded patients with pre-existing mental health problems or developmental delays. This analysis did not alter the primary study results, as the direction of change on composite scores remained consistent.

As with our study, a meta-analysis by LeBovidge showed more internalizing symptoms and fewer externalizing symptoms in patients with JIA (SpA, systemic JIA, oligoarticular JIA, etc.) compared to controls. (7) The authors also found that somatic complaints were a primary driver of internalizing symptoms in multiple studies. We question whether these somatic symptoms could simultaneously be dampening externalizing symptoms. However, we recognize that externalizing behaviors are the result of a complex interplay between social, familial, and physical factors and this is beyond the scope of this project to assess.

A number of mechanisms are likely involved in the relationship between disease activity and mental health: arthritis-associated physical disability, pain, fear, stress of having a medical diagnosis, and also the possibility of inflammation directly impacting brain functioning which is emerging as a major field of research. (6)(25)(28)(29)(30)(31) Over 80% of the cohort we studied were treated with medications, and almost 50% were on combination therapy with a DMARD and biologic. Continued work on understanding mental health in rheumatologic conditions will help us better understand how to best treat these diseases and their overlapping psychological/psychiatric problems. In the meantime, most data points toward better outcomes in patients who are treated aggressively. (32)

Parents of patients with SpA and PolyA (6/111, 5%) gave positive answers on history of self-harm, suicidal ideation, and/or suicide attempts which was significantly higher in the PolyA group compared to the normative population. Suicide is the second leading cause of death among youth, and children with chronic medical conditions are twice as likely to present with suicide risk than healthy controls. (33)(34) The American Academy of Pediatrics (AAP) recommends yearly screening for depression and recognition and management of suicide risk by primary care providers. (35) Since patients with arthritis see their rheumatologist every few months (which is more frequent than their primary care visits), screening can lead to earlier identification and intervention. Interestingly, though, a survey of pediatric rheumatology providers showed that only 2% performed universal screenings with a standardized instrument for depression, anxiety, and suicidal risk (36) despite the fact that patients of specialty clinics could be equally or at greater risk of para-suicidal symptoms. (37) Our study has confirmed the same finding and reinforces the need for suicide screening, especially for youth with PolyA.

Study strengths and limitations

To the best of our knowledge, our study is the first to examine behavior and mental health in the specific JIA populations of SpA and PolyA. CBCL forms were completed at or shortly after the cJADAS10 assessment to align psychological scores with arthritis scores. We thought that we would discover new patterns by separating the JIA subtypes; but unfortunately, we did not discover anything new using this approach and our findings parallel prior studies (4)(7).

Our study has important limitations. First, the majority of our patients were on arthritis medications and had low disease activity scores, which limits the generalizability of our results to relatively quiescent arthritis. Future studies should aim to enroll newly diagnosed patients prior to treatment as this may provide more information about mental health during a period of higher inflammation. Another important limitation is that CBCL reports are filled out by parents.

This may lead to an underestimation of symptoms by parents especially in light of the finding of high internalizing symptoms. It will be important for future studies to include surveys of the patients to better understand the scope and frequency of these internalizing symptoms. (24)(38)(39). Additionally, the socioeconomic status data was poorly filled out by our study participants, so we were not able to adequately control for confounding in this study. Lastly, as a result of this being a cross-sectional study, we cannot determine a causal relationship between arthritis disease activity and psychopathology.

Conclusion:

This study adds to the growing body of literature indicating that children with arthritis may be at increased risk for psychiatric problems. Specifically, this study indicates pediatric patients with SpA and PolyA have functional impairments and more internalizing symptoms, especially those with higher cJADAS10 scores. Externalizing symptoms are less frequent than that found in the healthy population and do not appear to be influenced by disease activity. Since these SpA and PolyA patients have more internalizing symptoms and less overt (i.e., externalizing symptoms), this poses a challenge for clinicians to identify mental health problems without formal screening procedures. Especially of concern is that PolyA patients are at an increased risk of self-harm/suicidality. These results emphasize the importance of mental health screening in pediatric patients with arthritis, especially when their disease is active, and it highlights the need for further studies into the mechanisms driving this psychopathology to better identify and treat psychiatric comorbidities.

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Table 1: Demographic and clinical characteristics of patients with spondyloarthritis or polyarthritis included in the study.

	Spondyloarthritis (n=53)	Polyarthritis (n=58)	P value
Demographic characteristics			
Age at CBCL (years)	14.0 +/- 3.0	13.0 +/- 6.0	0.222
Age at diagnosis (years)	11.5 +/- 4.1	6.6 +/- 6.9	<0.001
Duration of illness since diagnosis (years)	1.8 +/- 3.6	6.6 +/- 7.9	<0.001
Sex			0.006
Male	26 (49)	14 (24)	
Female	27 (51)	44 (76)	
Race/ethnicity ^a			0.766
Non-Hispanic White	21 (40)	26 (45)	
Non-Hispanic Black	1 (2)	0	
Non-Hispanic Asian	6 (11)	3 (6)	
Hispanic	11 (21)	17 (29)	
Other	9 (17)	6 (10)	
Unknown	5 (9)	6 (10)	
Clinical characteristics			

Taking arthritis medications ^b	44 (83)	54 (93)	0.099
NSAID alone	8 (15)	6 (10)	
DMARD +/- NSAID	9 (17)	9 (16) ^c	
Biological agents alone +/- NSAID	20 (38)	21 (36)	
Combination of DMARD and biological agents	7 (13)	18 (31) ^c	
Medical comorbidities ^d	32 (60)	25 (43)	0.069
HLA-B27			<0.001
Positive	18 (34)	1 (2)	
Negative	23 (43)	16 (27)	
Not done	12 (23)	41 (71)	
JADAS	3.9 +/- 5.7	2.6 +/- 6.1	0.962
Physician global assessment	0.5 +/- 1.8	0.5 +/- 1.8	0.405
Parent global assessment	1.5 +/- 3.2	1.6 +/- 2.4	0.712
Active joint counts	0 +/- 1.0	0 +/- 3.0	0.819

Data are presented as number (%) for categorical variables, and median +/- interquartile range for continuous variables.

^aSelf-reported race and ethnicity

^bArthritis medication includes NSAID, methotrexate, TNF inhibitor, sulfasalazine, tocilizumab, abatacept, leflunomide, tofacitinib, oral steroids, janus kinase (JAK) inhibitors, and mycophenolate mofetil.

^cOne of the patients in each group was taking JAK inhibitors in addition to other arthritis medication.

^dMedical comorbidities are defined as any current medical diseases through chart reviews and CBCL questionnaires, excluding psychiatric and developmental disorders. Examples include celiac disease, inflammatory bowel disease, uveitis, cataract, chronic renal disease, Raynaud's disease, psoriasis, migraines, asthma, fibromyalgia, etc.

Table 2: Age and sex adjusted differences in CBCL raw scores^a between patients with spondyloarthritis or polyarthritis and controls.

	Spondyloarthritis (n=53)		Polyarthritis (n=58)	
	Adjusted difference (with reference to controls) ^b	P value	Adjusted difference (with reference to controls) ^b	P value
Total competence	-1.5 (-2.7 to -0.3)	0.018	-1.6 (-2.8 to -0.5)	0.006*
Internalizing problems	1.5 (0.0 to 2.9)	0.047	1.9 (0.5-3.3)	0.007*
<i>Anxious/depressed</i>	<i>0.0 (-0.8 to 0.7)</i>	<i>0.916</i>	<i>0.6 (-0.2 to 1.3)</i>	<i>0.144</i>
<i>Withdrawn/depressed</i>	<i>0.4 (-0.2 to 0.9)</i>	<i>0.206</i>	<i>0.2 (-3.1 to 0.7)</i>	<i>0.439</i>
<i>Somatic complaints</i>	<i>1.2 (0.7 to 1.7)</i>	<i><0.001*</i>	<i>1.2 (0.7 to 1.6)</i>	<i><0.001*</i>
Externalizing problems	-2.7 (-4.5 to -0.9)	0.004*	-1.9 (-3.7 to -0.2)	0.033
<i>Rule-breaking behavior</i>	<i>-1.1 (-1.8 to -0.3)</i>	<i>0.004*</i>	<i>-1.1 (-1.8 to -0.4)</i>	<i>0.002*</i>
<i>Aggressive behavior</i>	<i>-1.6 (-2.8 to -0.4)</i>	<i>0.012*</i>	<i>-0.8 (-2.0 to 0.4)</i>	<i>0.189</i>
Total problems	-3.3 (-8.1 to 1.6)	0.191	-0.3 (-5.0 to 4.4)	0.906
<i>OCD problems</i>	<i>-0.1 (-0.6 to 0.4)</i>	<i>0.684</i>	<i>0.4 (0.0 to 0.8)</i>	<i>0.075</i>
<i>Self-harm^c</i>	<i>0.8 (0.1-5.9)^b</i>	<i>0.817</i>	<i>3.6 (1.3-9.6)^b</i>	<i>0.011*</i>

Data are presented as point estimates (95% confidence interval).

Scores in bold are primary outcome measures.

Scores italicized are subscales (exploratory analyses)

*Statistically significant p values with the level of significance set at 0.013, which is equal to 0.05 divided by 4 to account for multiple comparisons within the primary categories (i.e. primary outcomes)(in bold), and 0.05 for exploratory/subcategory measures.

^aRaw scores are used to account for the full-range variation.

^bage and sex adjusted

^cLogistic regression model for a binary outcome derived from two CBCL problem question 18 (deliberately harms self or attempts suicide) and question 91 (talks about killing self); result is presented as odds ratio (95% confidence interval).

Table 3: Adjusted differences in CBCL raw scores^a, by clinical 10-joint Juvenile Arthritis Disease Activity Score (JADAS), in patients with spondyloarthritis or polyarthritis.

	Spondyloarthritis (n=53)		Polyarthritis (n=58)	
	Adjusted difference by each point increase in JADAS ^b	P value	Adjusted difference by each point increase in JADAS ^b	P value
Total competence	-0.4 (-0.6 to -0.1)	0.009*	-0.3 (-0.5 to -0.1)	<0.001*
Internalizing problems	0.5 (0.1 to 0.9)	0.007*	0.3 (0.0 to 0.7)	0.088
<i>Anxious/depressed</i>	<i>0.3 (0.1 to 0.5)</i>	<i>0.004*</i>	<i>0.1 (-0.1 to 0.3)</i>	<i>0.482</i>
<i>Withdrawn/depressed</i>	<i>0.1 (-0.1 to 0.3)</i>	<i>0.179</i>	<i>0.1 (0.0 to 0.2)</i>	<i>0.045*</i>
<i>Somatic complaints</i>	<i>0.1 (-0.2 to 0.3)</i>	<i>0.167</i>	<i>0.1 (0.0 to 0.2)</i>	<i>0.038</i>
Externalizing problems	0.0 (-0.2 to 0.3)	0.710	0.0 (-0.2 to 0.3)	0.766
<i>Rule-breaking behavior</i>	<i>0.0 (-0.1 to 0.1)</i>	<i>0.836</i>	<i>0.1 (0.0 to 0.2)</i>	<i>0.094</i>
<i>Aggressive behavior</i>	<i>0.1 (-0.1 to 0.3)</i>	<i>0.528</i>	<i>0.0 (-0.2 to 0.2)</i>	<i>0.743</i>
Total problems	1.0 (0.1 to 1.8)	0.023	0.6 (-0.4 to 1.5)	0.218

Data are presented as point estimates (95% confidence interval).

Scores in bold are primary outcome measures.

Scores italicized are subscales (exploratory analyses)

*Statistically significant p values with the level of significance set at 0.013 which is 0.05 divided by 4 for outcome measures in bold, and 0.05 for other measures.

^aRaw scores are used to account for the full-range variation.

^bAdjusted for JADAS, age, sex and medical comorbidities.

Figure 1. Variations of CBCL total competence, internalizing problems, externalizing problems and total problems T scores with clinical 10-joint Juvenile Arthritis Disease Activity Score (JADAS).