

WITHIN-DAY VARIABILITY OF
PAIN IN YOUTH WITH
JUVENILE IDIOPATHIC ARTHRITIS
AND NON-ARTHRITIC
PAIN CONDITIONS

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ABSTRACT

Purpose: Describe and explain patterns of within-day variability of pain intensity in youth with JIA and non-arthritic pain conditions and within-day relationships between physical activity, mood and pain intensity.

Methods: Two complementary studies were conducted. In Study 1 pain intensity data previously collected 3 times per day for 7 days from 112 youth age 8 to 18 years with juvenile idiopathic arthritis (JIA) were examined for within-day patterns using cosinor analysis and generalized estimating equations (GEE). In Study 2, an electronic diary application for the iPod Touch was developed to collect momentary pain and mood data 7 times per day for 4 days from 28 youth age 8 to 17 years with JIA (n=11) or non-arthritic pain conditions (n=17). Physical activity data were collected by accelerometry. GEE analysis was used to examine relationships between pain intensity, physical activity and mood.

Results: A cosine pattern of systematic variability in pain intensity was identified in 22.4% of youth in Study 1 (n=85) and 25% in Study 2 (n=28). Age (Study 1: $\beta=0.28$, $p=0.039$), and diagnosis of systemic onset JIA (Study 1: $\beta=2.46$, $p=0.022$) were significant predictors of a cosine pattern of systematic variability. Within-day patterns of pain other than a cosine pattern are identifiable, as time of day (TOD) was a significant predictor of pain on GEE. The relationship between TOD and pain intensity differed by sex and disease subtype (Study 1). On average males had a higher probability of having moderate or severe pain in the morning compared to other times of day. On average females exhibited a U shaped within-day pain pattern with a higher probability of moderate to severe pain in the morning and evening and lower probability in the afternoon. Youth with enthesitis, psoriatic or undifferentiated subtypes of JIA had higher probability of moderate to severe pain in the evening; whereas for all other subtypes this probability was highest in the morning. Pain intensity was related to physical activity level; however, this relationship varied by time of day (Study 2 - combined JIA and non-JIA data). Youth had a higher probability of moderate to severe pain if they were sedentary in the morning, or more physically active in the evening. Higher pain intensity

was significantly related to negative mood ($\beta=1.16$; $p=0.004$ [Study 2]) and higher numbers of body locations in pain ($\beta=0.75$, $p<0.001$ [Study 2]).

Conclusions: Pain intensity varies by time of day for youth with JIA. This research identifies several within-day patterns that differ by sex and JIA subgroup. Physical activity and mood were associated with within-day fluctuations in pain intensity for youth with JIA and non-arthritic pain conditions. This research provides a foundation for future studies on the clinical relevance of pain variability for predicting treatment response and disease course as well as the development of physical activity interventions for youth with JIA and non-arthritic pain conditions. The Vulnerability Perturbation model of pain is presented for future research on temporal dynamics of pain.

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DEDICATION

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For my husband, Will, who frequently reminds me that this is one small part of a great adventure.

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OPERATIONAL DEFINITIONS

Acrophase: The timing of the high point of a mathematical model of a rhythm ⁽¹⁾

Allodynia: Pain due to a stimulus that does not normally provoke pain ⁽²⁾

Amplitude: Half the distance between the highest and lowest values of a mathematical model of a rhythm ⁽¹⁾

Chronobiology: The study of biological rhythms ⁽³⁾

Circadian: Period lasting approximately 24 hours ⁽³⁾

Cosinor Analysis: Least squares regression analysis method that fits a cosine curve to a time series. ⁽¹⁾

Diathesis: An organic predisposition to development of a chronic illness ⁽⁴⁾ or an illness or injury that causes an episode of acute pain which predisposes an individual to development of a chronic pain condition. ⁽⁵⁾

Diurnal: Part of the circadian period occurring during the day ⁽³⁾

Hyperalgesia: Increased pain from a stimulus that normally provokes pain ⁽²⁾

Idiopathic: Of or relating to a disease having no known cause. ⁽⁶⁾

Juvenile Idiopathic Arthritis: Arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks; other known conditions are excluded. ⁽⁷⁾

Mesor: The value about which oscillation of a rhythm occurs ⁽¹⁾

Nociception: The neural process of encoding noxious stimuli ⁽²⁾

Nocturnal: Part of the circadian period occurring during the night ⁽³⁾

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage ⁽²⁾

Pain Interference: The hindrance of life activities as a result of pain; for example, interference of engagement in social, cognitive, emotional, physical, or recreational activities or the interference with sleep or enjoyment of life. ⁽⁸⁾

Pain Threshold: The minimum intensity of a stimulus that is perceived as painful ⁽²⁾

Pain Tolerance: The maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation ⁽²⁾

QWERTY - The standard layout of a computer keyboard ⁽⁶⁾

Time-series: A series of observations taken sequentially in time ⁽⁹⁾

Youth: For the purposes of this study, the term "youth" is inclusive of adolescents and children between the ages of 8 and 18

LIST OF ABBREVIATIONS

ANOVA – analysis of variance
APPT - Adolescent Pediatric Pain Tool
BMI - body mass index
CHAQ - Childhood Health Assessment Questionnaire
ESR - erythrocyte sedimentation rate
FAS - Facial Affective Scale
GEE – generalized estimating equations
ICC - interclass correlation coefficient
ILAR - International League of Associations for Rheumatology
JIA – juvenile idiopathic arthritis
ml - millilitres
mm - millimetres
MVPA - moderate to vigorous physical activity
hr - hour
OR - odds ratio
PAQ - Physical Activity Questionnaire
PAQ-A - Physical Activity Questionnaire for Adolescents
PAQ-C - Physical Activity Questionnaire for Older Children
PedsQL - Pediatric Quality of Life Questionnaire
PGADS – physician global assessment of disease severity
PHV - peak height velocity
PInGo - Pain Information on the Go electronic diary
RF - rheumatoid factor
SES - socioeconomic status
SK - Saskatchewan
TMJ - temporomandibular joint
TOD – time of day
U of S – University of Saskatchewan
VAS - visual analogue scale
VDS - Vulnerability Diathesis Stress

CHAPTER 1

1 INTRODUCTION

1.1 General Background

Juvenile Idiopathic Arthritis (JIA) is among the most common chronic disabling diseases of childhood. ⁽¹⁰⁾ JIA can affect afflicted youth with an unpredictable course of pain and long-term disability. ^(11, 12) Pain negatively impacts quality of life ⁽¹³⁻¹⁵⁾ and participation in school and social activities, ⁽¹⁶⁾ thereby having a detrimental effect on normal childhood development. ^(17, 18) Although youth with JIA display a wide range of clinical presentations, pain is a common symptom with the majority of youth reporting pain on a daily basis. ^(19, 20)

Persistent pain seldom stays at a constant intensity; rather, pain can come and go or fluctuate in intensity. Youth with JIA report variability of pain intensity both within and across days. ^(16, 19-22) Attention to variations in pain intensity is important in a clinical setting as pain intensity can be used to determine possible sources of pain aggravation and help guide treatment. ^(23, 24) Pain intensity reports can be affected by biological (e.g. severity of injury or disease), psychological (e.g. anxiety), social and environmental factors (e.g. presence of peer or parent) with multiple influences that may vary throughout the day. ^(25, 26) To date the within-day variability of pain intensity in youth with JIA has not been thoroughly described, nor examined for potential contributing factors.

Within-day variability in pain may reflect the influences of variables that fluctuate either systematically in a pattern that is repeated daily, or irregularly with non-repeating fluctuations. Pain intensity in adults with arthritis shows systematic within-day variability ⁽²⁷⁻²⁹⁾ and the within-day pain patterns differ by subtype of disease. For example, morning pain is characteristic

of rheumatoid arthritis (RA) while osteoarthritis (OA) pain tends to peak in the evening.^(27, 30) Within-day pain patterns are recognized as a distinguishing feature between these two common types of adult arthritis and are consistent and robust despite severity of disease or treatment effects.^(27, 30) If systematic variability in pain intensity is identified among youth with JIA, this presents an important issue for accurate measurement in studies that score pain by recall of usual pain over a given period of time. Pain intensity at the time of reporting has a known biasing effect on recalled pain scores⁽³¹⁾; therefore, time of day of pain measurement may have a confounding influence on study findings.

Although the exact causes of within-day pain patterns are not fully understood, several biological variables known to affect nociception have been shown to demonstrate predictable circadian variability. Endogenous cortisol is a hormone with a number of important functions, one of which is to down-regulate the immune and inflammatory response resulting from exposure to injury, infection or physical or psychological stress.⁽³²⁾ In healthy individuals, cortisol displays a circadian rhythm with a peak early in the morning and a steady decline throughout the remainder of the day.⁽³³⁾ The absence of the normal early morning peak production of cortisol has been proposed as one possible explanation for the early morning peak of symptoms in adults with rheumatoid arthritis.⁽²⁸⁾ Proinflammatory cytokines that promote nociception, such as interleukin-6 (IL-6), also display circadian variability in healthy adults.^(34, 35) Pain intensity reports from youth with JIA have not yet been explored for within-day systematic variability.

Non-repeating within-day fluctuations in pain may result from the influence of situational and behavioural factors. Individuals with arthritis and other inflammatory musculoskeletal pain conditions report pain with physical activity.⁽³⁶⁻³⁸⁾ There are several reasons why physical activity may be associated with increased pain. In the peripheral tissues, joint inflammation causes increased sensitivity of both nociceptive and non-nociceptive pathways through lowered firing thresholds and activation of normally silent mechanosensitive afferent fibres.⁽³⁹⁾ This results in pain with movement and palpation. Changes in the central nervous system are also activated in the presence of ongoing peripheral pain and inflammation with expanded neuron receptor fields, increased efficiency at the somatosensory synapses, reduced inhibition of nociceptive firing and increased sensitivity of spinal cord afferent neurons to stimulation of both

inflamed and healthy tissues.^(39, 40) This would result in pain during normally innocuous physical activities. Contractures of tissues surrounding the joint as a result of prolonged or poorly managed inflammation could also contribute to pain with activity in that normal activities of daily living would move the joint to the end of available range.

In healthy adults, physical activity results in short-term systemic activation of the immune response^(41, 42) with increased IL-6 production in proportion to the intensity and duration of physical activity.⁽⁴³⁾ Intensive physical activity may result in increased circulating levels of IL-6 up to 100 times the baseline level, resulting in a pro-nociceptive environment.^(34, 41) The immune response to physical activity in youth with JIA, in whom baseline IL-6 levels are elevated, is unknown.

Physical inactivity has also been inconsistently associated with increased pain in youth. Several studies have found a positive association between pain and sedentary activities, particularly prolonged positions with computer use,^(44, 45) while others have found no association between the type of activity and the prevalence of neck pain.^(46, 47) However, these studies used cross-sectional survey designs and self-reported measures of activity and inactivity. No studies were found that examined the relationship between pain and inactivity in youth that used longitudinal designs or objective monitoring of physical activity with motion sensors. Physical activity and inactivity may both contribute to within-day fluctuations in pain; however, to date the short-term relationships between physical activity, inactivity and pain have not been examined in youth with JIA or other non-arthritic persistent pain conditions.

Psychological and cognitive variables such as stress and mood are situational variables known to affect pain reports that are subject to within-day variations.^(48, 49) Youth with JIA show a strong correlation between mood and pain intensity from day to day in which higher pain intensity is associated with more negative mood.^(16, 50) However, the within-day covariance of mood and pain intensity has not been examined. Within-day variations in mood may contribute to within-day pain fluctuations.

Social and environmental contexts vary throughout the day. School or work environments provide different distractions and demands compared to the home environment and those of extra-curricular activities. Although correlations between pain intensity and social or physical environment have been identified in cross-sectional or experimental pain studies,⁽⁵¹⁻⁵³⁾ no

prospective studies have been identified that examined the influence of social or physical environment on within-day variability in pain.

Studies investigating the variation of pain intensity in children with JIA have primarily utilized daily or weekly recall measures of pain,^(20, 54-57) cross-sectional study designs and between-person analytic methods.⁽⁵⁸⁻⁶¹⁾ While these study designs have been helpful for explaining some of the between-person variability of pain, they are unable to explain within-person and within-day variability. Although situational factors have been recognized as potential contributors to pain intensity variability,⁽²⁶⁾ there are currently no theoretical models available to guide hypothesis development to examine factors that may contribute to within-day fluctuations in pain or between-person differences in magnitude or patterns of pain variability.

1.2 Rationale for the Study

Greater understanding of within-day variability of pain intensity will expand our knowledge of the pain experience for youth with JIA and non-arthritic pain conditions and may lead to the development of novel therapeutic approaches for the management of pain. Pain fluctuations can be distressing for young patients who may see pain as a sign of disease aggravation or tissue damage, or feel frustration due to the interference of pain with activities. It is important to understand the range of within-day variations in the pain experience in order to effectively support and reassure young patients with arthritis and their families of the expected symptom experience.

Systematic variability in pain may point to previously unrecognized underlying disease mechanisms. In addition, systematic variability could be a source of measurement bias for recalled measures of pain that do not standardize for time of day of measurement as the intensity of pain at the time of recall has a known biasing effect on recalled pain scores. In studies investigating systematic variability in adult arthritis, OA and RA display different within-day patterns of pain. Therefore, this study will investigate differences in pain variability between JIA disease subtypes.

Individuals who experience within-day systematic variability (patterns of pain intensity that are repeated from day to day) may differ in significant ways from those who experience variability that is not systematic (irregular fluctuations) and from those whose pain is fairly consistent throughout the day. The contribution of demographic and disease variables to the

prediction of within-day systematic pain patterns will be examined. The relationship between pain and activity and pain and mood will be examined for their possible contribution to irregular fluctuations in pain. Subgroups of within-day variability may indicate an additional source of previously unrecognized heterogeneity in the population which may influence treatment response and outcome trajectories.

Factors contributing to within-day irregular fluctuations in pain have yet to be identified. Adults and youth with JIA and other non-arthritic pain conditions have identified physical activity as an aggravating factor. There are many barriers to physical activity participation for young people; however, pain with activity is an added barrier in this population. It is important to understand the short-term relationship between activity and pain in order to support youth with pain conditions as they become more physically active and to identify interventions that reduce pain during activity.

1.3 Study Scope and Purpose

The purpose of this research was to describe and explain the within-day variability of pain intensity in youth with JIA and non-arthritic pain conditions. Pain intensity reports were examined for systematic variability (time of day effect). In addition, the short term relationships between physical activity and pain and mood and pain were examined. This research also investigated the relationship between daily cortisol profile and pain patterns to determine if individual differences in cortisol profile are associated with systematic variability of pain intensity.

Two complementary studies were undertaken towards this purpose. In Study 1, pain intensity data collected by Stinson et al. for one week in a study on the construct validity of an electronic diary ⁽¹⁹⁾ were analyzed for within-day variability using cosinor analysis and generalized estimating equation (GEE) approach. This analysis was conducted to describe the within-day variability of pain intensity reported by youth with JIA, to determine if there was systematic variability of pain intensity, and to characterize subgroups identified by individual differences in pain variability. In Study 2, participants were recruited from a clinical sample of youth with JIA and a comparison group of youth with non-arthritic persistent pain that did not meet the JIA diagnostic criteria. Participants provided self-reports of pain and mood seven times per day for four days using a novel electronic diary application built for the iPod Touch (Apple

Inc.). In addition, participants provided twice daily saliva samples for cortisol measurement and were objectively monitored for physical activity over four days using accelerometers. The purpose of the second study was to describe the short-term relationships between pain and physical activity and mood, and determine if altered daily cortisol profile was associated with within-day variability of pain intensity. A comparison group of youth with non-JIA persistent pain conditions such as persistent low back pain or idiopathic wide spread joint pains was included in order to compare group differences in pain variability for the purposes of future hypothesis development. For example if distinct within-day pain patterns were identified between youth with JIA and those with non-arthritic pain conditions, this would suggest that underlying inflammatory disease processes may be contributing to pain patterns.

1.4 Objectives, Hypotheses, Questions

Study 1 Title: Within-day variability of pain intensity in youth with Juvenile Idiopathic Arthritis (JIA)

1.4.1 Study 1 Objectives

The objectives of Study 1 were:

[Objective 1.1] to describe the systematic within-day variability of pain intensity in a clinical sample of youth with JIA using 24 hour cosinor analysis

[Objective 1.2] to characterize subgroups with different patterns of daily variation based on cosinor analysis using logistic regression. The following variables were screened for inclusion in the analyses: demographic (age, sex), and physical variables (Physician Global Assessment of Disease Severity [PGADS], duration of disease, total number of active joints, JIA subtype)¹.

[Objective 1.3] to determine if time of day is a significant predictor of pain intensity controlling for the effects of age, sex, disease severity, disease duration, total number of active joints, and disease subtype using GEE.

¹ Variables chosen for analysis were selected from those that were available in the dataset provided and based on the literature review as being potentially relevant predictors of differences in pain intensity.

1.4.2 Study 1 Questions and Hypotheses

Objective 1.1 Questions:

- 1.1.1 What is the percentage of youth exhibiting a statistically significant 24 hour cosinor pattern in a pain intensity time-series?
- 1.1.2 What are the mean and range of mesor and amplitude² of the significant 24 hour cosine rhythms?
- 1.1.3 What are the frequencies of morning, afternoon and evening acrophase in the significant rhythms?

Objective 1.2 Hypothesis:

- 1.2 Logistic regression: Those with higher age, female sex, higher PGADS, higher total number of involved joints and systemic onset JIA will have a higher odds of having a significant 24 hour cosine rhythm to pain intensity (systematic variability of pain intensity).

Objective 1.3 Hypothesis:

- 1.3.1 GEE - Main Effects: time of day will be a significant predictor of pain intensity controlling for age, sex, PGADS, total number of joints involved and disease subtype.
- 1.3.2 GEE - Interactions: the effect of time of day on pain intensity will vary by disease subtype and by sex.

Study 2 Title: Explaining within-day variability of pain in youth with JIA and non-arthritic persistent pain

1.4.3 Study 2 Objectives

The objectives of Study 2 were:

[Objective 2.1] to describe the systematic within-day variability of pain intensity in the two clinical groups (JIA and non-JIA) using 24 hour cosinor analysis.

² See Operational Definitions section for definitions of mesor, amplitude and acrophase

[Objective 2.2] to characterize subgroups with different outcomes from the 24 hour cosinor analysis (significant and non-significant). The following variables were screened for inclusion in the logistic regression analysis: demographic (age, sex, maturation, body mass index [BMI], socioeconomic status [SES], disability [Childhood Health Assessment Questionnaire - CHAQ], general physical activity [Physical Activity Questionnaire - PAQ]), and disease variables (group, duration of disease, erythrocyte sedimentation rate [ESR], cortisol profile).

[Objective 2.3] to determine if time of day, mood and physical activity predict pain intensity controlling for age, sex, maturation (peak height velocity [PHV]), BMI, SES, group (JIA or non-JIA), disease duration, ESR, disability and cortisol profile (individual regression slope) using GEE analysis.

1.4.4 Study 2 Questions and Hypotheses

Objective 2.1 Questions:

- 2.1.1 What is the percentage of statistically significant 24 hour cosinor analyses in the pain intensity time-series?
- 2.1.2 What is the average and range of mesor and amplitude of the significant 24 hour cosine rhythms?
- 2.1.3 What are the frequencies of acrophase at each time of day in the significant rhythms for the JIA and non-JIA groups?

Objective 2.2 Hypotheses:

- 2.2 Logistic regression: Those with higher age, female sex, post maturation (post-PHV), higher BMI, longer disease duration, higher CHAQ, higher ESR, the JIA group and those with flat cortisol profile will have higher odds of having a significant 24 hour cosine rhythm to pain intensity (systematic variability).

Objective 2.3 Hypotheses:

- 2.3.1 GEE – Main Effects: Time of day and negative mood will be significant predictors of higher pain intensity.

2.3.2 GEE - Interactions: There will be a parabolic relationship between activity and pain intensity in that highest physical activity and lowest physical activity categories will be associated with highest pain intensity while moderate physical activity and low inactivity will be associated with lowest pain intensity.

2.3.3 GEE - Interactions: The effect of time of day on pain intensity will differ by group and sex.

2.3.4 GEE - Interactions: The effects of physical activity on pain intensity will differ by group, sex and time of day.

CHAPTER 2

2 LITERATURE REVIEW

The goals of this research were to describe and explain within-day variations in pain intensity in youth with JIA and non-arthritic pain conditions with an examination of systematic variations in pain and the short-term relationship between physical activity and pain. To our knowledge, there are no theoretical models that provide a framework for examining temporal dynamics of pain. Therefore, the principles of chronobiology⁽⁶²⁾ were used to inform the study design and research question development for both studies. A novel theoretical model for examining temporal dynamics of pain is presented in Chapter 6. The theoretical foundations for this model primarily come from a bibehavioral model for children's pain proposed by McGrath and Hillier and the Vulnerability-Diathesis-Stress model of Dworkin, Hetzel and Banks.^(5, 26) The various theoretical models contributing to the development of the Vulnerability Perturbation model and the principles of chronobiology will be reviewed in Theoretical Foundations in Chapter 3.

The literature review will focus on the following topics:

- 1) An overview of the epidemiology, etiology and factors predicting disease outcomes in JIA. This section will also review the epidemiology of pain in youth with JIA and factors contributing to between-person and within-person variability of pain in this population.
- 2) The measurement and assessment of pain in youth, and use of electronic real-time data capture for pain assessment.
- 3) Within-day variability of pain and systematic variations in pain in animal and human experimental and clinical models, and a review of common methods of analysis used to examine within-day pain variability.

- 4) Factors of interest as potential contributors to within-day pain variability, with a focus on endogenous cortisol, physical activity, and emotional affect/mood.

2.1 Section 1: Juvenile Idiopathic Arthritis and the Prevalence of Pain

2.1.1 Diagnosis

JIA is among the most common chronic rheumatologic diseases of childhood. ^(10, 63) The International League of Associations for Rheumatology (ILAR) defines JIA as chronic inflammation in at least one joint for a minimum of six weeks with onset prior to the age of sixteen years. Diagnosis is made by clinical exam in association with laboratory tests and after exclusion of other causes of arthritis. There are seven distinct subtypes of JIA: systemic, oligoarthritis, polyarticular rheumatoid factor positive, polyarticular rheumatoid factor negative, enthesitis-related, psoriatic and undifferentiated. ⁽⁷⁾ See Appendix A for JIA Subtype Classifications.

2.1.2 Incidence and Prevalence

Epidemiological studies on the incidence and prevalence of JIA vary widely depending on the population studied and methods of case ascertainment. Adam et al., using a nationally representative weighted sample from the 1996 Canadian National Population Health Survey found a prevalence of arthritis and rheumatism of 7 per thousand among 12 to 19 year old youth. ⁽⁶⁴⁾ This prevalence is inclusive of other rheumatic diseases of childhood such as juvenile dermatomyositis and juvenile systemic lupus erythematosus. A review by Manners and Bower reporting on data from 34 epidemiological studies undertaken between 1966 and 1998 found world-wide prevalence values for JIA, juvenile chronic arthritis or juvenile rheumatoid arthritis ranging from 0.07 to 4.01 per thousand children with incidence rates ranging from 0.008 to 0.226 per thousand children per year. ⁽⁶⁵⁾ The central reason identified for differing prevalence values and incidence rates between studies was the method of case ascertainment. Community based studies, which would include previously undiagnosed cases, reported higher prevalence and incidence rates than studies based on clinical records, identifying a substantial proportion of youth that do not attend specialist services for joint pain and inflammation.

In western Canada, the prevalence of childhood arthritis is approximately 0.36 per 1000 First Nations children and 0.20 per 1000 Caucasian children (based on a clinical sample using the 1977 Juvenile Rheumatoid Arthritis [JRA] diagnostic criteria).⁽⁶⁶⁾

2.1.3 Etiology

The exact causes of JIA are unknown but there is a growing body of literature to support the view that JIA is a complex subset of autoimmune diseases with both genetic and environmental risk factors affecting the immune and inflammatory regulatory systems.^(10, 67, 68) Single nucleotide polymorphisms (SNPs) at the Human Leukocyte Antigen (HLA), Protein Tyrosine Phosphatase, Non-receptor Type 22 (PTPN22), and V-set Domain Containing T Cell activation inhibitor 1 (VCTN1) regions have been associated with the risk of developing some subtypes of JIA.^(68, 69)

There is less conclusive evidence to identify environmental risk factors for the disease, primarily due to difficulty conducting adequate prospective studies given the low incidence rate and heterogeneity of disease subtypes which result in small sample sizes and low statistical power.⁽⁶⁷⁾ Several studies have identified childhood infections as a risk for development of JIA. Aslan et al. identified a higher incidence of enteric bacterial infections in JIA cases compared to healthy controls.⁽⁷⁰⁾ Rubella, parvovirus⁽⁷¹⁾ and streptococcal infections have also been identified as a possible triggers for onset or exacerbation of JIA.⁽⁷²⁾ In a review on the effects of major stressful life events, such as divorce or death in the family, and chronic minor psychological stressors, authors Herrmann et al. identified 1 prospective and 8 retrospective studies published between 1954 and 1997.⁽⁷³⁾ All 9 studies supported the conclusion that psychological stressors were associated with the initiation and exacerbation of juvenile arthritis³ and no studies were identified that contradicted this conclusion.

Other environmental contributing factors recognized for their potential contribution are maternal smoking during pregnancy as a risk factor and breastfeeding as a protective factor.^(67, 74) High exposure to tobacco smoke during pregnancy was associated with a two times higher

³ These studies used the terms Juvenile Idiopathic Arthritis, Juvenile Chronic Arthritis and Juvenile Rheumatoid Arthritis depending on the diagnostic criteria employed. The term juvenile arthritis is used here to be inclusive of all three terms.

risk of childhood arthritis in female offspring, but not male offspring.⁽⁷⁵⁾ Results of studies on breastfeeding are contradictory and limited by small sample size.⁽⁶⁷⁾

2.1.4 Factors Predicting Outcome

Factors predictive of a poor long-term prognosis vary among subtypes. Oen et al. in a review of 393 patients from three Canadian rheumatology practices, identified a young age of disease onset as predictive of a longer active disease duration in youth with pauciarticular arthritis (4 or fewer joints) and rheumatoid factor negative (RF-) polyarticular disease.⁽⁷⁶⁾ However, young age of onset was associated with a shorter active disease duration for youth with systemic onset arthritis. Male sex was predictive of higher functional disability for youth with systemic onset arthritis, but with less functional disability for youth with in RF- and RF+ polyarticular disease. Youth living on First Nation reserves had higher disability than urban living peers regardless of race indicating that social and environmental factors such as place of residence impact disease outcomes.⁽⁷⁶⁾ On clinical assessment and medical record review of 268 patients from a single Norwegian rheumatology practice, Flato et al. found young age of onset, long duration of elevated inflammation, positive RF status, and a larger number of affected joints to predict longer active disease duration. Joint erosions were additionally predicted by the absence of certain HLA genetic markers and symmetric disease activity. In this study, physical disability was predicted by female sex, symmetric arthritis, early hip joint involvement, prolonged elevated inflammation and positive RF status.⁽⁷⁷⁾

2.1.5 Disease Course

JIA follows an unpredictable course of flares and remissions.⁽¹²⁾ There are three general patterns of disease activity; monophasic, polycyclic and persistent. The monophasic pattern is a single episode of disease activity lasting less than 24 months followed by remission without recurrence. Polycyclic disease is multiple cycles of disease activity of any duration interrupted by periods of inactive disease. Persistent disease is defined as active disease lasting greater than 24 months. Singh-Grewal et al. reported that in a sample of 45 youth with systemic onset JIA followed for approximately 5 years, 42 percent of youth experienced a monophasic pattern, seven percent polyphasic and 51 percent persistent disease.⁽¹²⁾ Persistent disease was also associated with polyarticular onset and ongoing systemic disease persisting at 3 months and 6

months follow-up.⁽¹²⁾ Fantini et al. followed a sample of 683 youth with oligoarthritis, polyarticular arthritis, systemic arthritis and juvenile spondyloarthropathies for 10 years and found 28 percent had monophasic disease, 10 percent polycyclic and 62 percent persistent disease.⁽⁷⁸⁾ In this study, sex and age of onset did not predict remission. Remission rates differed across disease subtypes. Youth with polyarticular disease were least likely to achieve remission and those with juvenile spondyloarthropathy most likely to achieve remission. Patients referred to specialized rheumatology services less than one year after symptom onset also had a higher rate of remission than those referred between 1-5 years or more than 5 years from disease onset.

2.1.6 JIA Clinical Presentation and Management

Although there are a wide range of clinical presentations, many affected youth endure chronic pain and long-term disability.⁽⁷⁹⁾ The primary symptom complex of JIA includes pain, fatigue and stiffness.^(16, 80) JIA is also often associated with severe joint destruction, growth anomalies, musculoskeletal impairments leading to functional disability, psychosocial consequences such as depression and lower quality of life and extra-articular disease manifestations.^(10, 80)

In the absence of a cure, treatment for JIA is focused on achieving remission by reducing the severity of the disease, managing symptoms and disease consequences. The ideal treatment approach for management of JIA involves a multimodal, multidisciplinary approach that includes pharmacological, physical and psychological interventions.⁽⁸⁰⁾ Pharmacologic management may include analgesics and nonsteroidal anti-inflammatory medications, intra-articular steroid injections, systemic glucocorticoid therapy, disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents such as tumor necrosis factor inhibitors.^(10, 80)

The goals of physical interventions are to reduce symptoms and prevent or improve musculoskeletal impairments, general physical activity participation and functional capacity.^(80, 81) Physical interventions may include physical therapy or occupational therapy for therapeutic exercises, general exercise prescription, manual therapy, electrophysical or thermal modalities, education, splinting or bracing, or acupuncture. Psychological interventions are indicated for patients for whom the psychosocial impact of the disease interferes with quality of life or emotional or physical functioning. Youth and their families who require support in developing

coping skills, managing pain, depression, anxiety or stress may benefit from referral to a psychologist.⁽⁸⁰⁾

2.1.7 Pain with JIA

Pain from arthritis is thought to primarily stem from chemical inflammatory mediators in the synovial fluid of the inflamed joint, such as nerve growth factors, bradykinin, prostaglandins, substance P and cytokines that sensitize the afferent nociceptive nerves.^(39, 82, 83) This causes a lowered firing threshold of the afferent nociceptors and increased sensitivity to normally innocuous stimuli such as movement and touch (allodynia) as well as spontaneous firing of nociceptors causing pain at rest.⁽⁸⁴⁾ This is referred to as nociceptive pain. Pain from arthritis may also result from neuropathic mechanisms due to changes in peripheral nerves and/or the central nervous system as a result of ongoing peripheral inflammation and tissue sensitization.^(40, 85, 86) Central sensitization perpetuates the lowered nociceptive firing thresholds even in the absence of ongoing inflammation.⁽⁸⁵⁾ Changes at multiple levels along the central nervous system nociceptive pathways, such as the dorsal horn of the spinal cord, spinothalamic tracts and cerebral cortex, are implicated in central sensitization's role in allodynia and increased pain on movement with arthritis.⁽⁸⁷⁾ A recent study identified neuropathic pain symptoms in a large subgroup of community dwelling adults with OA.⁽⁸⁸⁾ Although similar studies with youth with JIA have not been conducted, it is possible that pain in this population stems from a combination of nociceptive and neuropathic mechanisms.

Pain is a common symptom for youth with arthritis.⁽⁸⁹⁾ The large majority of youth with JIA presenting for routine clinical visits report pain.⁽⁹⁰⁾ Schanberg and Anthony, in a study using daily diaries for eight weeks, found that children with polyarticular arthritis reported pain on 73 percent of days and only five percent of children reported no pain during the study period.⁽²⁰⁾ These findings have been supported by daily diary studies involving all JIA subtypes⁽⁹¹⁾ and those involving higher frequency monitoring.⁽¹⁹⁾ Although the majority of youth with JIA report mild pain,^(16, 19) approximately one third of daily pain reports exceed an intensity of 40 mm on a 100 mm visual analogue scale (VAS).⁽²²⁾

Pain and disability from arthritis can have significant social and emotional consequences for the child or adolescent in that it can interfere with school participation, activities of daily living and leisure time activities, as well as increase dependence on parents, thus impacting

normal childhood development. ^(18, 92, 93) Pain is associated with greater psychological distress, depression, and anxiety, ^(64, 94, 95) and has a significant negative relationship with health related quality of life in youth with arthritis. ⁽¹³⁻¹⁵⁾

2.1.7.1 Between-person factors associated with pain intensity in JIA

Studies investigating factors associated with the pain experience in youth with arthritis have largely utilized cross-sectional and between-person methods of analysis. Considerable variability in pain reports has been observed between youth with arthritis and investigations into factors contributing to between-person variability have been inconsistent.

Physician-rated disease severity has been found to be moderately associated with pain intensity ratings in several studies with correlations ranging between $r=0.44$ and $r=0.65$. ^(54, 96-98) However, in regression models, JIA disease activity has been found to explain only a minority of the total variance in pain intensity. ^(22, 54)

The effect of prolonged disease activity on the pain experience over time is unclear. In regression models, some authors have found that longer disease duration explains a small portion of the variance in pain intensity, ⁽⁵⁴⁾ while others have found no significant relationship between pain and disease duration. ⁽⁹⁹⁾ Longer disease duration has also been associated with lower pain frequency. ^(55, 100)

The child's age and sex also have been inconsistently associated with pain intensity with both positive associations ^(54, 98) and no association. ^(22, 58, 101) Depressive symptoms, negative mood and stressful events have been associated with pain reports on both cross-sectional ^(16, 20, 50, 94) and longitudinal studies in youth with arthritis. ⁽⁹⁵⁾

Between-person analysis has been used to explore some of the factors associated with pain intensity and identify characteristics of individuals that may be more likely to experience pain. However, it is important to ensure that factors associated with between-person variability in pain are not incorrectly interpreted as within-person effects as these two methods of analysis can result in opposing conclusions. ⁽¹⁰²⁾

2.1.7.2 Within-person factors associated with pain intensity in JIA

Within-person analysis of repeated measures of pain may provide some insight into pain variability that cannot be determined from a between-person study design. Within-person

analysis utilizes the patient as his or her own control for factors such as personality, genetic differences and reporting biases. ⁽¹⁰³⁾

Several studies have investigated the within-person inter-relationships between psychosocial factors and pain intensity. Depression symptoms have been found to predict pain intensity at 6 and 12 months follow-up for those whose pain was initially in the mild to moderate range. ⁽⁹⁵⁾ Child anxiety, depression and maternal distress have been found to account for almost half of the variability in pain intensity on longitudinal follow up. ⁽¹⁰⁴⁾ Daily mood was related to pain intensity in that more positive mood was related to lower pain intensity. ^(16, 50)

2.1.8 Summary

JIA is a heterogeneous cluster of inflammatory diseases of childhood affecting approximately 1 in 1000 youth. The disease follows an unpredictable course that extends into adulthood for approximately half of youth diagnosed. Genetic predisposition coupled with numerous biological and psychosocial environmental factors contribute to disease onset and perturbations. Youth with JIA present with varied clinical manifestations of the disease which may impact physical and emotional functioning and quality of life. Pharmacologic, physical and psychological therapies are indicated to control inflammatory disease activity, manage symptoms of pain, stiffness, fatigue, and minimize the physical and psychological consequences of the disease. Pain is a common symptom in youth with JIA and variability in pain intensity has been reported both within and across days. Numerous demographic, disease related, and psychological factors contribute to the pain experience for youth with arthritis; however, only a small portion of the variability in pain intensity has been explained.

2.2 Section 2: Measurement and Assessment of Pain in Youth

2.2.1 Pain Measurement and Assessment

Pain intensity is the most frequently measured aspect of the pain experience in both clinical and research settings. However, it has long been recognized that pain intensity is only one component of the pain experience. Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." ⁽¹⁰⁵⁾ Pain is a

multidimensional experience and a thorough assessment of pain includes measurement along domains addressing pain intensity, sensory characteristics, affective qualities, cognitive evaluative and behavioural responses to pain in order to capture as complete a picture as possible of the lived experience. ^(96, 106, 107)

Measurement of pain in children is particularly challenging depending on the verbal and cognitive capacity of the child to effectively self-report such a complex, abstract concept. ⁽¹⁰⁸⁾ The meaning of pain scores and interpretation of pain scale anchors is individually determined and dependent on past exposure to pain, reflection on the consequences of a high or low score, and the social environment. ^(51, 108, 109) However, most children over the age of 8 years with typical cognitive development are capable of providing self-report of aspects of the pain experience (intensity, affect, interference with activities) using a VAS or other age-appropriate scale in a paper-based or electronic format. ^(108, 110)

Since the pain experience is influenced by numerous internal and external environmental factors, as these states change, pain also changes in intensity, quality, unpleasantness and location. This provides an additional challenge for the measurement of persistent pain in that the various components of the pain experience are not constant over time and may fluctuate independently of one another. For example, a child with arthritis may have increased pain intensity for a brief period of time as she engages in physical education class at school, although the distraction of the game minimizes the unpleasantness of the increased pain. New locations of pain may emerge during the activity, and although the pain intensity may remain elevated for several hours, the interference of pain with activities decreases when the activity ends and the demands on the child are altered.

2.2.2 Electronic Diary Methods of Data Capture

Out of necessity, measurement of persistent pain for clinical purposes relies largely on retrospective recall of symptom levels. However, our understanding of the complexity of the pain experience is reduced when youth are asked to summarize their pain experience over long periods of time. Many clinicians resort to daily pain diaries in an attempt to capture the variability of pain experienced by their patients. There are no current guidelines for analysis and interpretation of within-day or between day pain variability for clinical purposes, although attempts have been made to provide a framework for analysis. ⁽¹¹¹⁾

Studies of pain in children with JIA have primarily used daily or weekly recall measures of average pain intensity. ^(16, 54-56, 100, 112) Retrospective recall of pain scores requires complex cognitive processes of retrieving painful experiences from memory which are influenced by the attention given to pain over the course of the day. ^(31, 113) Recall also requires summarization and reconstruction of many pain experiences over a period of time and cognitive strategies vary between individuals. ⁽¹¹⁴⁾ Although children over the age of seven years are generally accurate in recalling average and worst pain over a one day and one week period, ⁽¹¹³⁾ recall scores are biased by the length of the period of recall, worst pain and most recent pain score provided during the recall period. ^(31, 115, 116)

Concern over the influence of recall bias on the validity of pain scores, and an impetus to improve the convenience of data collection and data quality has led to the recent development of electronic diaries for the assessment of current pain (momentary pain) which have been used in both adult ⁽¹¹⁷⁻¹²⁰⁾ and child populations. ^(19, 55, 100, 121)

Electronic diaries employ multiple momentary measurements of pain over a series of days which allow for symptom monitoring in the natural environment (i.e. home, school, work). Studies involving adults or children report improved compliance, improved data accuracy and an absence in errors of omission with the use of electronic diaries compared to paper and pencil diaries. ^(118, 122) The multiple momentary measures of electronic diaries allow for a more detailed picture of the daily pain experience and are useful for an investigation of the dynamic nature of pain and analysis of the association between pain and time-varying factors such as physical activity.

Several studies have been conducted on pain in children using electronic diaries. Palermo et al. used an electronic diary with the Faces Pain Scale ⁽¹²³⁾ to collect daily pain intensity scores for 7 days from youth ages 8 to 16 years with JIA and headaches and compared these to paper diaries. ⁽⁵⁵⁾ Completion rates were significantly greater for the electronic diary compared to the paper diary. Paper diaries contained a greater number of errors and omissions compared to the electronic version. Stinson et al. reported good construct validity, usability and feasibility with an electronic diary developed for adolescents with JIA which captured pain intensity, body locations of pain, pain affect, pain interference (general and specific activities), verbal descriptors of pain, stiffness, fatigue, and treatments for pain. ⁽¹⁹⁾ Average weekly pain intensity

scores collected (3x/day for 2 weeks) with a 5 cm VAS on electronic diary had moderate correlations ($r=0.55$, $p<0.01$) with recalled pain intensity scores, a quality of life measure ($r=-0.44$, $p<0.01$) and showed sensitivity in detecting change in pain intensity following a joint injection. Connelly et al. used an electronic diary to collect data 3 times daily for 14 days to examine the relationship between daily stressors, lifestyle behaviours and headache occurrence in 25 youth ages 8 to 17 years.⁽¹²⁴⁾ Significant within-person associations were found for stress intensity and headache occurrence using hierarchical linear model analysis. For each standard deviation increase from the individual typical reported stress level, the relative odds of a new headache occurrence was 1.22 ($p=0.01$).

2.2.3 Summary:

Pain is a complex sensory and emotional experience that is influenced by biological, psychological, social and environmental factors. Multidimensional measures are the most appropriate for thorough assessment of pain. Changes in pain over time add to the complexity of scoring pain retrospectively. Electronic diary data capture methods have been developed and validated for pain assessment among youth with JIA. Electronic diaries are more convenient and accurate than paper-based diaries and minimize the biasing effect of retrospective recalled measures.

2.3 Section 3: Description and Analysis of Within-day Variability of Pain

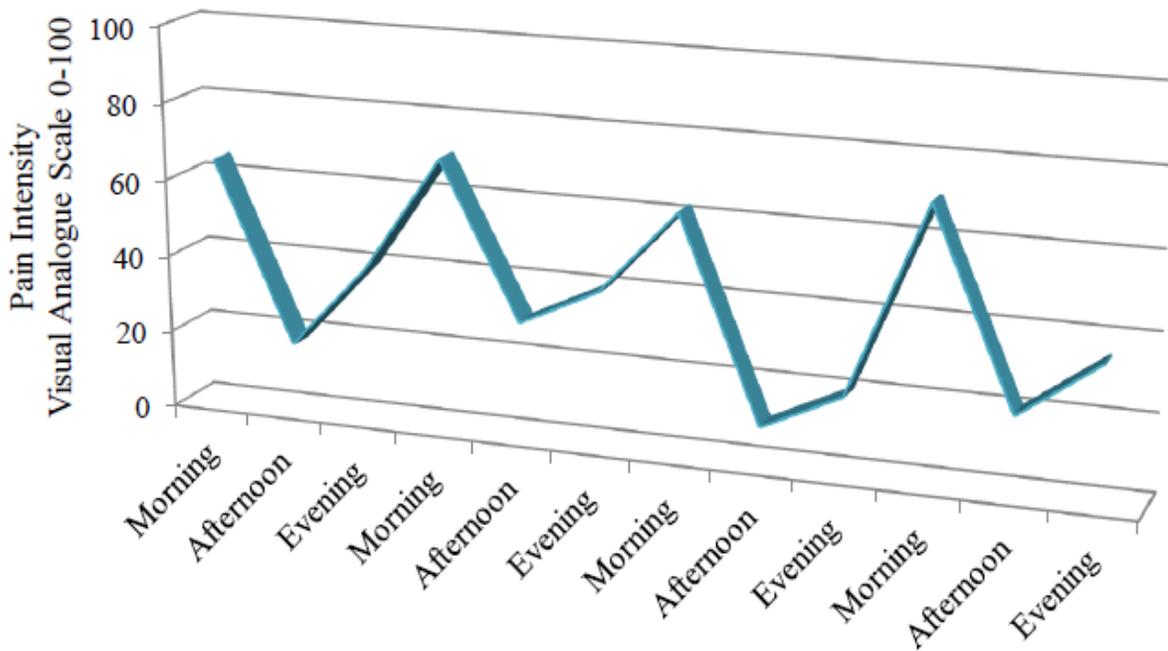
2.3.1 Definitions

Within-day variability of pain can be defined as noticeable changes in pain intensity, pain location, sensory descriptors of pain and/or pain interference occurring throughout the day. Multiple measures of pain over the course of the day and over a series of consecutive days are required to assess within-day variability. Within-day variability may take two forms: systematic variability or irregular fluctuations.

Systematic within-day variability in pain can be defined as a predictable change in a characteristic of the pain experience (intensity, location, sensory quality, or interference) that is observed to repeat in roughly the same pattern and at the same cycle frequency over the period of observation. For example, systematic within-day variability of pain intensity may take the form

of consistently higher intensity in the morning, followed by lowest intensity in the afternoon and a slight rise in intensity in the evening. Systematic within-day variability would exist if the pattern was seen to generally repeat from one day to the next (see Figure 2-1).

Figure 2-1: Hypothetical Example of Systematic Variability in Pain Intensity



A circadian pattern is one that repeats approximately every 24 hours, and ultradian patterns at less than 20 hours. ⁽⁶²⁾ Weekly, monthly, seasonal, yearly or longer patterns may also be considered cycles of systematic variability.

Irregular within-day fluctuations can be defined as noticeable changes in a characteristic of the pain experience throughout the day that are not repeated in a consistent and predictable daily pattern over the period of observation. Irregular fluctuations in pain likely result from the influence of time-varying factors that change in a non-systematic manner. For example, physical activity participation fluctuates throughout the day and may influence pain intensity. Multiple measures of pain throughout the day and over a series of consecutive days are required to assess irregular fluctuations in pain.

The research to date on within-day pain variability has been focused on pain intensity. Pain is seldom maintained at a constant intensity throughout the day and within-day changes in intensity of persistent pain have been well documented in both adult ^(24, 116) and pediatric populations such as JIA and headache. ^(19, 121)

In a clinical setting, patients are often asked to recall their usual pain or prospectively monitor changes in pain intensity. This information is considered clinically relevant to assess changes in patient status over time or evaluate treatment effect. Monitoring pain intensity fluctuations is also clinically useful to determine possible sources of pain aggravation or relieving factors that may assist in treatment planning. However, to date, variability in pain in youth with JIA has not been thoroughly described or investigated for systematic or irregular fluctuations, nor has there been an examination of factors influencing within-day variability in pain in this population.

2.3.2 Systematic Variability: Experimental Pain and Analgesic Effect

Changes in pain throughout the day have been explored in both animal and human experimental pain models as well as in clinical populations with particular attention paid to adults with rheumatoid arthritis (RA) and osteoarthritis (OA). ^(23, 125)

Animal studies have consistently demonstrated circadian variation in pain sensitivity and analgesic effectiveness throughout the day with lowest pain threshold (peak pain sensitivity) occurring during the early nocturnal activity phase. ⁽¹²⁶⁻¹²⁸⁾ Oishi et al. found that circadian variation in pain sensitivity of mice could be altered by a shift in the feeding schedule and that no circadian rhythm in pain sensitivity was detected in mice lacking the circadian clock gene (Clock-mutant mice). ⁽¹²⁹⁾ This suggests that circadian variation in pain sensitivity is primarily set by the genetically programmed biological clock but can be altered by environmental factors. However, caution must be taken in directly applying these findings to humans as rodents differ from humans in physiology, anatomy and behaviour, thus impacting both the measurement of pain and the underlying circadian variability in pain sensitivity.

Induced pain and clinical studies in humans do not show the same consistency in the existence or timing of peak pain sensitivity. Several authors found that pain response to experimental pain stimuli was greatest in the early morning, ⁽¹³⁰⁻¹³³⁾ while others found pain sensitivity to peak in the evening. ^(134, 135) Still others have found no evidence of time of day

effects on pain sensitivity.^(136, 137) In a recent review, Junker et al. speculated that the differences in timing of peak pain sensitivity between studies may be due to methodological differences in that diverse types of pain stimuli and tissue locations may manifest different timing of peak sensitivity.⁽¹³⁸⁾ Clinical populations also exhibit circadian rhythmicity in the timing of peak pain; however, differences in the timing of symptoms exist. For example, several authors have found that women in labour report higher pain levels in the evening or at night,⁽¹³⁹⁾ and pain from cancer is worse in the evening or at night.⁽¹⁴⁰⁾ Morning peaks are seen in pain from rheumatoid arthritis, fibromyalgia and myocardial infarction,⁽¹⁴¹⁻¹⁴³⁾ while osteoarthritis pain tends to peak in the evening.⁽¹⁴⁴⁾ In a study using a mouse model of neuropathic pain and a sham-operated control, Kusunose et al. identified a circadian rhythm in pain sensitivity in the neuropathic mice, but no time-dependent changes in pain sensitivity in the sham-control mice.⁽¹²⁸⁾ This supports the conclusion of Junker et al. that different sources of pain may result in distinct timing of peak sensitivity.⁽¹³⁸⁾

2.3.3 Systematic Variability: Adult Arthritis and Chronic Pain

Daily patterns of pain in adult arthritis are well known and are part of the clinical description and distinction between RA and OA.⁽¹²⁵⁾ Time-dependent daily patterns of pain have been identified in adults with RA,⁽³⁰⁾ OA,^(27, 36, 144) fibromyalgia,^(142, 145) idiopathic chronic pain,^(24, 146) and many acute pain conditions.⁽²³⁾ There is, however, a great deal of inter-individual variability to pain patterns within groups,^(24, 144, 147) and not all individuals display consistent patterns of pain.^(24, 148)

Bellamy et al. collected pain intensity scores 10 times per day for seven consecutive days in 20 adult patients with knee OA.⁽¹⁴⁴⁾ Although there was substantial variability in reported mean pain and range of pain scores between individuals, 15 of the 20 participants showed a significant time of day effect with one way analysis of variance (ANOVA) and 18 of the 20 participants showed a significant 24 hour rhythm to pain intensity using cosinor analysis. Sixteen of the 18 participants had peak pain in the afternoon or evening.

In contrast, Murphy et al. reported little within-day variation in pain severity in 40 women with hip or knee OA.⁽³⁶⁾ Pain intensity was rated on a five point categorical scale with verbal anchors of 0 (no pain) to 4 (extremely severe). The authors concluded that there was little within-day variability in pain, although they did not report on the method of analysis used to

make this conclusion. Pain scores were averaged across each time point for aggregate measures of pain. There are two possible reasons for this study to conclude minimal within-day variability. First, a 5 point categorical scale is less sensitive to small but noticeable changes in pain. Also, aggregation of scores across the 40 individuals would most likely result in a deviation towards the mean that might mask inter-individual differences in the effect of time of day on pain.

Bellamy et al. collected self-reported pain intensity and stiffness scores and a manual dexterity performance task six times per day for 10 consecutive days from a sample of 21 adults with hand OA. ⁽²⁷⁾ Fifteen of the 21 participants showed a significant 24 hour rhythm to pain intensity on cosinor analysis. Self-reported stiffness and manual dexterity performance also showed significant 24 hour rhythm on cosinor analysis in the majority of participants. Pain intensity was lowest in the early afternoon for the majority of participants. The circadian variation in pain intensity was detectable despite differences in mean pain, disease status, medication use, age, sex, and occupation among participants.

In a similar study, Bellamy et al. collected self-reported pain intensity and stiffness scores and a manual dexterity performance task six times per day for seven consecutive days in a sample of 14 patients with RA of the hand and 14 healthy age and sex matched controls. ⁽³⁰⁾ Using cosinor analysis, they found significant 24 hour rhythms in pain intensity, stiffness and manual dexterity over the week long observation period. Peak pain and stiffness occurred in the morning for all patients. Both patients and controls demonstrated significant 24 hour patterns in manual dexterity with peak performance occurring in the early afternoon.

Several clinical studies investigated the association between demographic or disease variables and circadian variation in pain reports. Bellamy et al. collected self-reported pain, stiffness and fatigue scores six times per day for 10 consecutive days from 21 women with fibromyalgia. ⁽¹⁴²⁾ Pain threshold using dolorimetry was also measured. Ten of the 21 participants showed a significant 24 hour rhythm in pain intensity with cosinor analysis. Subgroup analysis revealed that those participants who were more sensitive to mechanical pressure pain (lower pain threshold with dolorimetry <2.25kg pressure) were more likely to show a significant cosine rhythm to pain intensity. Eight of 12 participants who were more sensitive to pain (lower threshold <2.25kg) had a positive 24 hour cosine rhythm of pain compared to 2 of 9 participants were less sensitive to pain (higher threshold >2.25kg).

Jamison and Brown collected hourly pain intensity ratings for one week from 189 adults with chronic pain.⁽²⁴⁾ Using polynomial regression of pain intensity scores, participants were classified into 6 daily patterns (pain profiles). Approximately two-thirds of participants had a significant daily pattern, with the majority of patterns being upward or downward linear patterns. Twenty-six percent of participants had no significant pattern to their daily pain intensity scores. Although sub-group analysis was not reported, the authors stated that the location of pain affected the likelihood of having a pain pattern with upper extremity affected patients being less likely to have a consistent pain pattern. Another interesting finding from this study was that participants who scored higher on the Symptom Check List (SLC-90-R) for anxiety, depression and emotional distress were more likely to have a flat or random within-day pain profile compared to those with lower SLC-90 scores.

2.3.4 Systematic Variability: JIA

There is evidence of within-day patterns of pain intensity, interference, stiffness and fatigue in adolescents with JIA. Pain intensity is generally highest in the morning for youth with arthritis, with girls more likely than boys to have worst pain in the morning.^(50, 91) Stinson et al. using an electronic diary to measure symptoms three times daily for two weeks in (n=112) adolescents with all subtypes of JIA, found peak pain interference and stiffness in the morning while fatigue had a U-shaped daily pattern with peaks in the morning and evening.⁽¹⁹⁾ In the same study, average weekly pain intensity was correlated with pain interference (Week 1 $r = 0.59$, Week 2 $r = 0.77$; $p < 0.01$); however, no association between time of day and pain intensity was reported. An earlier study by Stinson et al. involving youth with JIA concluded that there was no significant time of day effect on pain intensity.^(110, 149) The aim of that study was to evaluate the usability of an electronic diary with qualitative methods and therefore a small purposive sample of adolescents (2 cycles of n=10) was included. If within-day patterns of pain differ by subtype, as is the case in adult arthritis and experimental models of pain, then the aggregated analysis of all disease subtypes in these studies may have confounded the ability to detect time of day effects on pain intensity.

2.3.5 Analysis of Within-day Changes in Pain

2.3.5.1 General challenges

Traditional summary statistics, such as measures of central tendency or variance, do not make full use of the data, do not provide the desired information on the time-varying nature of pain, and are typically poor descriptors of the pain and variance due to the skewed distribution that is common in pain data.^(150, 151) Time-series analysis methods are capable of providing simple and efficient summary descriptions of the variance observed in the data and identifying systematic within-day variability of pain.

Analysis of repeated measures of pain data collected over multiple time points presents three general challenges.⁽¹⁵²⁾ Primarily, repeated measures collected from the same individual are not statistically independent which is a violation of the basic assumptions of many traditional analysis methods.⁽¹⁵³⁾ Time-series may also present serial dependence of measures. When scores are collected repeatedly over a period of time, proximal observations tend to be more closely related than those more temporally distant.⁽¹⁵³⁾ For example, patients report that they have "good days" and "bad days," and pain scores recorded on the same day may be more strongly correlated than scores reported several days or weeks apart.

Secondly, self-reported data collected in the natural environments of the participants are very rarely complete and it is common to have data missing at random or covariate-dependent missingness.⁽¹⁵²⁾ Although investigators frequently ignore this issue, unequal numbers of measures per participant violates the assumption of heteroskedasticity (equal variances), thereby restricting the use of methods requiring balanced datasets unless imputation methods or weighted analysis options are employed.^(153, 154)

Finally, repeated measures of pain data do not typically have a normal distribution.^(155, 156) Although pain is common for youth with arthritis, symptoms may come and go throughout the day, and vary in intensity when present. The resulting distribution has both dichotomous properties (pain/no-pain) and continuous scaling qualities (varying severity of pain when present).⁽¹⁵⁷⁾ The distribution properties vary between individuals and may range from normal to highly skewed. Distributions approximate normal as the frequency and intensity of pain increases.⁽¹⁵⁸⁾ Non-normal distributions can be statistically managed in a number of ways. Non-parametric statistical methods can be utilized, statistical transformations can be attempted to

modify the distribution to approximate normal, linear variables can be converted to categorical, or more robust statistical methods such as multilevel modelling can be employed. ^(153, 154)

2.3.5.2 Within-day analysis

Methods used to analyze within-day variability of pain from data collected multiple times per day can generally be classified into one of three categories: pooled analysis, two-stage procedures, and multilevel analysis. Systematic variability in pain is captured by evaluating a time of day effect on pain when symptoms are reported multiple times per day at generally the same time points over a series of days. Irregular fluctuations in pain are described by measures of variability or by evaluating the relationship between pain and time-varying factors. The following three sections will describe the pooled, two-stage and multilevel analysis methods found in the literature for examination of within-day pain variability and will outline the limitations of these methods.

2.3.5.3 Pooled analysis

Aggregation approaches pool data from several time points from one individual or across individuals and explore time of day differences using simple t-tests or ANOVA on the pooled data. ^(159, 160)

Murphy et al. collected pain scores from 40 women with hip or knee osteoarthritis (OA) and 20 healthy women six times per day for five days. ⁽³⁶⁾ Scores were aggregated across individuals and across days to examine change in pain over the course of the day. No time of day effects on pain intensity were found; however, the statistical method used to examine time of day effects was not reported.

Similarly, Okifuji et al. found no difference between morning, afternoon and evening pain reports collected for 30 days from adult women with fibromyalgia when data were pooled across individuals for each time of day. ⁽¹⁶¹⁾ Similarly, the statistical method used to examine time of day effects was not reported in this study.

Van Grootel et al. collected pain scores four times per day for 14 days from 133 adults with temporomandibular joint (TMJ) pain. ⁽¹⁶²⁾ Pain scores were aggregated within-individuals for each time of day in order to determine the time of peak pain for each individual in order to categorize participants by time of day of peak pain. Repeated measures analysis of variance

(RMANOVA) was then used to examine time of day effects on pain. They found a bimodal distribution of peak time of pain with the majority of participants experiencing peak pain after lunch and only 21 percent of participants experiencing peak pain in the morning.

Using a non-aggregation pooled method, Soriani et al. analyzed the time of occurrence of 2517 migraine attacks reported by 115 school aged children over a 12 month period.⁽¹⁶³⁾ Circadian and seasonal variability in the timing of headaches was analyzed using a partial Fourier series on count data. The authors found both a seasonal and circadian rhythm in the timing of headache onset. The seasonal peak occurred in December and there were two daily peaks, the main peak occurring in the late afternoon and the secondary peak in the early morning. This method of analysis can be used on count data, such as headache occurrence counts; however, it cannot be used to investigate variability in pain intensity with a continuous or categorical scale.

2.3.5.3.1 Limitations of pooled analysis

Although aggregation of scores is an acceptable exploratory method to determine group time-of-day effects on pain,⁽¹⁵⁹⁾ aggregation across individuals does not allow differing subgroup specific variations in time-of-day effect to emerge. This was illustrated by van Grootel et al. who used a combination of aggregation and multilevel analyses to find a bimodal distribution of peak timing of pain in a homogeneous sample of adults with TMJ pain.⁽¹⁶²⁾ Experimental pain models also reveal differences in circadian rhythms of peak pain sensitivity suggesting that a heterogeneous population should be expected to exhibit different subgroups of timing of peak pain. In addition, pooled analysis methods are limited in the complexity of inferences that can be made and do not make full use of the richness of the data that has been collected.^(154, 159) For example, person-level data such as demographic or disease characteristics of participants cannot be evaluated for associations, interactions or confounding influence on the relationship between pain and time of day except by stratified analysis.

2.3.5.4 Two-stage procedures

Two-stage procedures are used to describe individual change over time, assess inter-individual differences in change, identify subgroup patterns of change, and explore person-level influences on change characteristics.^(154, 164, 165) In the first stage, a separate regression of the

dependent variable with the factors of interest is conducted for each individual. The individual regression coefficients are then entered as dependent variables in the second stage regression to examine relationships between first stage regression parameters and person-level factors of interest.⁽¹⁵⁴⁾

Singer and Willet recommend the following steps in the analysis of individual change over time.

(1) Begin with visual inspection of a graphical plot to explore each individual's course of change in the variable of interest over time. Visual inspection of subgroups of plots reveals general trends in the data and identifies individuals with unusual patterns of change. For large datasets, a random selection of cases can be visually inspected.

(2) Following visual inspection, a separate parametric regression model is fit to each person's data using a common functional form. The choice of regression function, be it linear or curvilinear, should be guided by theory and past research.

(3) Summary statistics or parameter estimates from each individual's regression model are collected and can be further analyzed with person-level demographic and disease characteristics to identify inter-individual differences in change. Two-stage regression has also been referred to as hierarchical regression and is recommended for repeated measures data analysis by a number of authors.^(103, 153, 154, 165) Although many two-stage regression methods have been used to analyze repeated measures of pain data,^(155, 156, 166) only two methods of person-level analyses were identified in the literature for the investigation of within-day pain variability: polynomial regression, and cosinor analysis.

2.3.5.4.1 Polynomial regression

Jamison et al. collected hourly self-reported pain scores from 186 adults with chronic pain for one week.⁽²⁴⁾ For each individual, pain scores were regressed against hour, hour squared and hour cubed to determine whether a linear, quadratic or cubic model best fit the change in pain over time. Participants were classified into one of six daily pain pattern categories: positive linear, negative linear, inverted-U, U curve, poly-curved, or no pattern depending on the most appropriate fitting regression model. The daily pain pattern categories were examined for differences in demographic and clinical variables using Chi-squared or ANOVA tests for the second stage of the hierarchical regression. The majority of participants had a positive or

negative linear pattern (43%), just under one in four patients (21%) had a curvilinear U-shaped or inverted-U pattern, and the remainder (36%) had a poly-slope or no slope pattern. There were no group differences on demographic variables; however, there were significant differences in pain site and emotional distress factors. Those with upper extremity pain were most likely to have a no slope pattern. Having no distinct pain pattern was significantly associated with greater emotional distress.

2.3.5.4.2 Cosinor analysis

Cosinor analysis, or the cosinor procedure, has been used to examine pain data for cyclicity, or repeating fluctuations over a single day or a series of days. The single cosinor procedure uses a least-squares regression to fit a cosine curve of a predetermined frequency to a time series of repeated measures data.⁽¹⁾ The single cosinor procedure is most often fit to a 24 hour cycle. The cosinor procedure produces three efficient and descriptive parameter estimates. These are: mesor, the middle of the fitted cosine; amplitude, the distance from the mesor to the peak or trough of the fitted cosine; and acrophase, the time of the peak of the fitted cosine. The test of statistical significance is the zero-amplitude test, which is an F-statistic that is a comparison of variances of the data about the fitted cosine curve to the variance about a straight line.^(1, 167) Rejection of the null hypothesis signifies that the fitted cosine curve approximates the data more closely than does a straight line with zero slope.^(1, 168)

Cugini describes cosinor analysis as "the most important method of periodic regression" for describing rhythms in biological data.⁽⁶²⁾ The primary benefit of cosinor analysis over other traditional regression procedures is in the production of the descriptive parameter estimates.^(62, 151) In addition, the cosinor procedure, if statistically significant, demonstrates systematic and predictable temporal variability of the data.⁽⁶²⁾ Cosinor analysis can be conducted with irregular sampling intervals and is robust against single outlier values.⁽¹⁶⁷⁾

A number of authors have used cosinor analysis to describe individual pain variability in adults with rheumatic diseases.^(27, 30, 142, 144, 147, 169) Even in these seemingly homogeneous populations not all participants displayed a significant cosinor rhythm in their daily pain variability. In addition, participants display variability in the timing of peak pain (acrophase) and magnitude of variation (amplitude) in pain during the day.

There are restrictions to the use of the cosinor procedure. The primary assumptions with cosinor analysis are that the underlying pattern is assumed to be sinusoidal with a fixed period length, phase and amplitude, and that the period length is known. ^(1, 170) Data requirements for cosinor analysis vary depending on the expected periodicity of the data, and time points of sampling should be based on sound logic to adequately capture variability. ^(151, 154) To observe a cycle, Nelson recommends four observation points over at least two cycles. ⁽¹⁾ Greater accuracy in true peak and trough times can be captured with higher sampling frequencies; however, the added burden for participants may not result in improved ability to observe the cycle. ⁽¹⁷⁰⁾ A study comparing the frequency of sampling for the estimation of parameters for temperature data found that sparse sampling affected the estimation of the amplitude more so than the acrophase and mesor. ⁽¹⁷¹⁾ De Prins recommends that other regression methods of analysis be used in conjunction with the cosinor procedure due to frequent violation of these stringent assumptions. ⁽¹⁷⁰⁾

2.3.5.4.3 Limitations of two-stage procedures

There are several general limitations to two-stage analysis procedures. Two-stage procedures are based on least squares estimations; however, pain data collected in the field frequently violate assumptions of these methods. Due to unequal sampling between participants, stage 1 regressions may have differing sampling variabilities that would be better estimated using maximum likelihood or quasilielihood estimation procedures. ⁽¹⁷²⁾ Although stage 1 regression accounts for within-person dependence in measures, it does not account for serial dependence that may be present in the data. ⁽¹⁵⁴⁾ Despite this, results of two-stage regression methods often yield very similar results to those of maximum likelihood procedures. ^(154, 165)

2.3.5.5 Multi-level analysis

Multi-level analytic procedures extend two-stage methods with simultaneous analysis of within-person and between-person variances. ⁽¹⁵⁴⁾ More advanced multi-level procedures also allow for the inclusion of multiple time-varying predictive factors in the model, unbalanced datasets and specification of a covariance structure that best depicts the data. ^(154, 165)

2.3.5.5.1 Repeated measures analysis of variance

Repeated measures analysis of variance and repeated measures analysis of covariance (RMANCOVA) are multilevel analysis methods in that they separate within-person and between-person variance.⁽¹⁵³⁾ These methods have been used to examine within-day variance of pain in youth with JIA.^(19,110, 149)

There are a number of limitations to ANOVA models for examining within-day variability in pain. They require a balanced dataset thereby requiring imputations or exclusion from analysis for participants with missing data.^(154, 173) ANOVA does not allow for inclusion of time-varying covariates,⁽¹⁷⁴⁾ and it assumes normal distribution and sphericity, or equality of correlations, between all measures taken from one individual.⁽¹⁷³⁾ ANOVA procedures also require equally spaced intervals between repeated measures.⁽¹⁷⁴⁾ Finally, ANOVA requires all independent variables in the model to be categorical and use a continuous dependent variable. Categorization of variables measured on an interval or ratio scale may result in a loss of information and biased conclusions if categorization is not based on sound theory and clinical relevance. Finally, and most importantly, a statistically significant outcome from an ANOVA or RMANOVA merely establishes a time of day effect. It does not describe the shape, amplitude, mean or phase of the rhythm.⁽¹⁶⁷⁾ Given these limitations, more descriptive analyses and more robust multilevel approaches are recommended for analysis of repeated measures data, and are essential for the analysis of associations between the dependent variable and time-varying covariates.^(153, 154, 165) These include the multilevel mixed effects models and GEE.

2.3.5.5.2 Multilevel mixed effects models

Mixed effects, random effects, fixed effects, and hierarchical linear modelling share the same principles, data requirements and limitations which will be outlined by discussing mixed effects models. While traditional regression models compute one intercept and slope to describe the average change over time observed in the data, mixed effects models include both fixed effects (factor has the same effect on all individuals) and random effects (different effect on each individual).⁽¹⁶⁵⁾ With mixed effects models, individuals can be assumed to vary randomly from the overall population average and separate intercepts and slopes for each individual can be calculated.⁽¹⁶⁵⁾ Mixed effects models can also handle a mixture of time-varying and time-

invariant covariates, and unbalanced data sets as long as the data are missing at random. ⁽¹⁷³⁾

Complex correlation structures can be specified in the model to account for autocorrelation and serial dependency. ⁽¹⁵⁴⁾ However, mixed effects models are most appropriate for continuous responses that are approximately normal in distribution. ⁽¹⁷⁵⁾

A study by Keefe et al. used multilevel mixed effects models to examine sex differences in within-day variance of pain, coping and mood in 100 adults with OA. ⁽¹⁷⁶⁾ Pain scores collected two times per day for 30 days were examined for within-person effects of time of day, mood and coping and between-person factors of sex and overall mean pain levels. Overall, pain scores were higher in the evening than the morning; however, there was an interaction between time of day and sex with females reporting a greater increase in pain across the day than males.

Several other studies have utilized multi-level modelling to investigate the association between pain and time-varying covariates but did not report time of day effects on pain. Okifuji et al. used mixed effects modelling to explore sequential relationships between pain, fatigue and emotional distress in 81 women with fibromyalgia but did not examine the effect of time of day on pain. ⁽¹⁶¹⁾ Sterling and Chadwick used multilevel modeling to examine the relationships between pain intensity, fear of pain, objectively monitored physical activity and trauma symptoms in a study of adults with chronic whiplash associated disorder. ⁽¹⁷⁷⁾ In this study, the authors screened for time of day effects on pain using linear regression. Since the linear relationship was not statistically significant, time of day was not included in the multilevel models. There are several problems with this approach. The assumption of independence for the regression is violated by repeated measures data, possible confounding differences in time of day subgroups are ignored and a linear relationship between pain and time of day is assumed although non-linear patterns may have been more appropriate for this population.

2.3.5.5.3 Generalized estimating equations

The GEE approach, developed by Zeger and Liang ⁽¹⁷⁸⁾ is an extension of the generalized linear model and can be used to model correlated repeated measures data when the dependent variable is not necessarily normally distributed. ⁽¹⁷⁹⁾ Similar to mixed effects models, GEEs allow specification of a working correlation matrix to account for specific within-person correlations in responses and produces population average estimates of changes in responses

with changes in covariate vectors.⁽¹⁷⁴⁾ GEEs can also handle missing data, continuous or categorical dependent variables, and static or time-varying predictor variables.⁽¹⁸⁰⁾

Bjorling used GEE to identify the relationship between momentary stress and headache pain intensity in adolescent girls with headache.⁽¹²¹⁾ Depression, headache frequency and daily stress levels were also examined for moderating effects on the time varying relationship between stress and headache intensity; however, the effect of time of day on pain was not explored.

2.3.5.5.4 Limitations of multilevel analysis

Similar to the ANOVA approach, multilevel analyses do not provide descriptive parameter estimates regarding the shape, amplitude, mean or phase of the rhythm. They merely establish that rhythmicity exists if time of day is found to be a statistically significant predictor variable.⁽¹⁶⁷⁾ Although multilevel analyses are robust in regards to unbalanced datasets and can handle different covariate data structures (continuous or categorical, static or time-varying), they can be more challenging to interpret. Mixed effects models are more sensitive to accurate specification of the correlation matrix compared to GEE.⁽¹⁸⁰⁾ However, overall, multilevel analyses are an efficient method for describing complex relationships between covariates. The choice between these methods depends on the research question and type of data available. Mixed effects models specify individual variation from the population average and can be used to compute individual level predictions. GEEs are more robust to mis-specification of the correlation matrix and are used to make population average predictions of response in the dependent variable to changes in the covariate vector.

2.3.6 Summary

Sensitivity to experimental induction of pain shows circadian variation. Rhythms in rodents are consistent and show peak pain sensitivity during the early activity phase which would correlate with the early morning in humans. Circadian rhythms can be modified in mice by altering environmental synchronizers or can be abolished in genetically modified mice that lack the Clock gene, indicating both genetic and environmental setting of circadian rhythms. Human experimental pain models do not display consistent rhythms which is likely a result of methodological differences between studies in the type and location of stimulus.

Both adults and youth with arthritis exhibit circadian rhythms in disease related symptoms. Pain intensity varies in distinct sub-type specific rhythms in adults with arthritis. However, the existence and timing of these rhythms is not consistent for all individuals and varies by location of pain and psychological factors such as depression and anxiety. Individuals with higher pain sensitivity with mechanical stimulation are more likely to display a circadian rhythm in clinical pain intensity. This may signify that pain variability indicates a susceptibility to symptom perturbations in vulnerable subgroups.

To date only a small portion of the variability of pain in JIA has been explained by between-person factors such as disease severity, inflammation, and psychological factors. However these studies did not account for time of day of assessment and possibly missed important factors of influence due to the study design. Within-day variations in pain have not been investigated for systematic circadian variation in youth with JIA and the association between pain and time-varying factors such as physical activity and mood have not been explored.

There are three general methods of analysis for within-day variability in pain: pooled, two-stage, and multi-level mixed methods. While each has strengths and limitations as a method for the analysis of within-day pain variability, two approaches have particular strengths for different purposes. For the description of systematic variability, cosinor analysis, as the first phase of a two-stage approach, produces three parameters that are highly descriptive of systematic within-day rhythms of pain. For the analysis of irregular fluctuations in pain and modelling of complex relationships between time-varying factors, multi-level analyses, either Mixed Effects Modelling or GEE offer an efficient approach. However, GEEs are more robust to mis-specification of the correlation matrix and are the appropriate method for analysis of non-normally distributed data.

2.4 Section 4: Explaining Within-Day Pain Variability

Pain is recognized as a multidimensional sensory and emotional experience influenced by biological, psychological and social factors. ⁽²⁵⁾ As such, it is expected that the within-day variations in pain can be explained by complex interactions between endogenous and exogenous factors and their influence on the nociceptive system. Endogenous factors are those physiological processes driven from within and synchronized by the “internal clock” that maintain a rhythm

even in the absence of environmental cues. ⁽³⁾ Exogenous factors are modifiable and responsive (negative feedback) or predictive (feedforward) of changes in the environment. ⁽¹⁸¹⁾

2.4.1 Systematic Variability

2.4.1.1 Physiological processes and biochemicals: endogenous cortisol

Physiologic processes and biochemicals related to pain such as cortisol, endorphins, enkephalins, substance P, melatonin, and inflammatory cytokines have demonstrated predictable circadian rhythms in healthy adults and children. ^(28, 29, 134, 182, 183) These rhythms are thought to be organized by the body's "internal clock" which, in humans, is located in the hypothalamic suprachiasmatic nucleus and synchronized with the light-dark and sleep-wake cycles. ⁽¹⁸⁴⁾

Healthy adults and children exhibit circadian patterns of opioid peptide (endorphins, enkephalins) production, which are higher in the morning and lower in the evening. ⁽¹⁸⁵⁾ Glucocorticoid (cortisol) production also follows a well-documented circadian rhythm. ⁽¹⁸⁶⁾ Cortisol acts to modulate the inflammatory response via a complex system of positive and negative feedback mechanisms between the hypothalamus, pituitary gland and adrenal cortex, also known as the hypothalamic-pituitary-adrenal axis (HPA axis). ⁽¹⁸⁷⁾ Cortisol and melatonin regulate the production of the proinflammatory and anti-inflammatory cytokines. ⁽¹⁸⁷⁾ Both hormones peak in the early morning shortly after waking and in the majority of individuals show a steady decrease over the remainder of the day in the absence of a significant external stimulating event. ^(187, 188) A number of proinflammatory cytokines exhibit diurnal rhythms in healthy subjects with peak concentrations late at night and in the early morning. ^(35, 189)

Adults with active RA exhibit altered functioning of the HPA axis. ^(28, 190) The inability of patients with active RA to mount a sufficient cortisol response to inflammation in the morning has been implicated as playing a role in the typically observed symptom pattern of peak pain in the morning. ⁽²⁸⁾ A study by Picco et al. involving youth with oligoarticular JIA in remission identified normal daily rhythms of plasma cortisol but an increased circulating level of the pituitary hormone adrenocorticotrophic hormone (ACTH) in the morning compared to controls. ⁽¹⁹¹⁾ ACTH is known to have an indirect inhibitory effect on pain through the stimulation of endogenous opioids and glucocorticoids. ⁽¹⁹²⁾ The authors concluded that children with inactive oligoarticular arthritis have dysregulation of the HPA axis, a partial resistance to ACTH, and

impaired circadian pattern of cortisol release. The clinical significance of this finding and the relationship between altered HPA axis function and pain in youth with active JIA has yet to be established.

2.4.1.1.1 Measurement of cortisol

Salivary cortisol is considered a superior measure to plasma cortisol for several reasons. ^(193, 194) First, and most importantly, saliva collection is a non-invasive, non-painful method of collection, whereas serum collection requires a blood-draw. Saliva collection is more appropriate for data collection in field based research, ⁽³³⁾ particularly for early morning and late evening sampling for children, as there is minimal interference with daily activities. Finally, there is a high correlation ($r=0.93$) between saliva cortisol concentration and serum unbound cortisol concentration, which is the physiologically active form of the hormone. ⁽¹⁹⁴⁾

2.4.1.1.2 Emotional affect and mood

Murray et al. studied positive and negative affect using both a normal ambulatory protocol and a desynchronization protocol. ⁽¹⁹⁵⁾ A desynchronization protocol requires participants to remain in controlled conditions in which all environmental synchronizers for timing of biological cycles, such as light-dark, activity and meal-times, are removed for several days in order to isolate the endogenous biological rhythm from the environmental cues. They found that in both the ambulatory and desynchronization protocols, positive affect had a significant circadian variation with an average peak at 14:00 hours and trough at 01:00 hours. Negative affect, on the other hand, had no significant circadian rhythm.

Monk et al. also found that with a forced desynchronization protocol circadian variation in mood, reasoning and mental attention was demonstrated in healthy adults. ⁽¹⁹⁶⁾ Similar to the work of Murray et al. this study showed a peak in positive mood in the mid to late afternoon. Although these studies were conducted with healthy adult participants and did not investigate the relationship between circadian variation in mood and pain, several authors have demonstrated an association between mood and pain in youth with JIA. ^(16, 50, 94, 95) Further elaboration on the possible role of mood on irregular fluctuations in pain will be provided in the following section.

2.4.2 Irregular Fluctuations

Fluctuations in activity levels, food consumption, psychological states such as mood or stress, and the social and physical environments are synchronized with the sleep-wake cycle and are subject to within-day variation.⁽³⁾ These factors may influence pain intensity scores in youth with JIA through their effect on attention to pain, anxiety, mechanical stress on inflamed structures, and changes in the biochemical nociceptive environment. Exogenous factors have inconsistent diurnal patterns except under standardized conditions and, though unlikely to result in systematic variability in pain intensity, may contribute to irregular pain fluctuations throughout the day.

2.4.2.1 Physical activity

All youth, including those with JIA and other painful conditions, are encouraged to participate in regular physical activity in order to maintain cardiovascular fitness, muscle strength and endurance, joint range of motion, bone health, physical function and quality of life.^(81, 197-199) However, compared to their healthy peers, youth with JIA demonstrate lower levels of total daily physical activity^(200, 201) and lower leisure time activity participation.^(60, 202) Youth with JIA have many inactivity related physical impairments including lower cardiovascular fitness,⁽²⁰³⁻²⁰⁵⁾ lower muscle strength,^(60, 206, 207) limitations in joint range of motion, osteopenia and osteoporosis, growth plate anomalies, and impairments in cardiac and pulmonary function.⁽²⁰⁸⁻²¹⁰⁾ Physical impairments are thought to result from a combination of reduced activity participation leading to deconditioning and muscle atrophy,^(205, 211, 212) as well as disease-related pathophysiological changes in the skeletal muscles, and cardiac and pulmonary function.⁽²¹²⁻²¹⁴⁾

Physical activity and inactivity have complex bi-directional relationships with pain that encompass changes in pain sensitivity and disease related symptoms with activity and changes in activity with increased pain.^(215, 216)

2.4.2.1.1 Activity modification due to pain

Pain is often reported as a barrier to physical activity participation for individuals with arthritis,^(217, 218) and functional disability is associated with higher levels of daily pain and higher percentage of days with pain in youth with JIA.⁽²⁰⁾ Adults with chronic wide-spread pain self-report lower activity levels than their peers.⁽²¹⁹⁾ On objective monitoring of physical activity

with accelerometers, adults with tension type headache have been observed to reduce physical activity following the onset of headache.⁽²²⁰⁾ In addition, pain affects muscle recruitment patterns through central mechanisms that include inhibition of muscles proximal to the painful area, and increased activation of muscles distal to the painful area resulting in altered motor behaviors during activity.^(215, 221) Altered motor behaviors as a result of pain have been identified as a further cause of increased pain with activity due to altered mechanical loading and overuse.⁽²¹⁵⁾

2.4.2.1.2 Change in pain sensitivity with activity

The short-term effect of physical activity on pain sensitivity to experimental pain differs between healthy populations and those with pain conditions. In general, resistance exercise of sufficient intensity reduces pain sensitivity in healthy populations, resulting in lowered pain scores with similar magnitude stimulation during and for a brief time following exercise.⁽²²²⁻²²⁴⁾ This effect is referred to as exercise induced hypoalgesia (EIH).⁽²¹⁵⁾ In contrast, adults with pain conditions generally experience increased pain sensitivity with exercise which is thought to result from impaired pain-inhibitory mechanisms.⁽²²⁵⁻²²⁷⁾ However, pain populations are not homogeneous in the response to exercise. Hoeger-Bement et al. found that women with fibromyalgia could be classified into three subgroups based on their pain response to isometric contractions of the elbow flexors.⁽²²⁸⁾ Approximately one third of participants had increased pain with the exercise and a corresponding increase in pain sensitivity to experimental pain, one third had EIH and decreased pain sensitivity and one third had no change in arm pain with the exercise. They found that women with higher baseline pain thresholds (less sensitivity) and older age were more likely to have increased pain with exercise.

2.4.2.1.3 Change in disease symptoms with activity and inactivity

The temporal relationship between physical activity and disease symptoms has been examined in adults and youth with various pain conditions. Kashikar-Zuck et al. found that in a group of 104 adolescents with juvenile primary fibromyalgia syndrome, those that were more highly active reported less pain on daily diaries over one week.⁽²²⁹⁾ Higher pain intensity co-occurs with higher daily physical activity levels in women with knee osteoarthritis,⁽³⁶⁾ and women with chronic fatigue syndrome.⁽³⁷⁾

Liszka-Hackzell and Martin collected pain reports every 90 minutes throughout the waking hours for three weeks from 15 adults with acute low back pain and 15 adults with chronic low back pain. ⁽³⁸⁾ In this study physical activity was objectively monitored using accelerometers. Ten of the 15 participants with acute low back pain showed significant cross-correlations between pain and physical activity where an increase in physical activity was followed by an increase in pain. On average, the increase in pain occurred within 30 minutes of the increase in activity. No significant relationship between pain and activity was found for those with chronic low back pain; however, lagged correlations were only examined within a 60 minute window and may not have been able to capture a longer delay in pain onset for participants with chronic pain. There were several methodological problems with this study which may have influenced the ability to detect a relationship between pain and physical activity in participants with chronic pain. Rather than summarize the accelerometry data across 90 minute windows, the authors sampled one minute epochs every ten minutes and performed cross-correlations with estimates of pain scores derived from cubic spline interpolations of the daily pain reports. This method of analysis does not account for serial dependency of repeated measures and it evaluates co-occurring activity and derived pain scores which are not necessarily representative of the true pain score occurring at that time.

The relationship between pain complaints and time spent in sedentary activities has been investigated by a number of researchers primarily using cross sectional study designs. In a community based nationally representative sample of adolescents, Hakala et al. found that neck and shoulder or low back pain prevalence increased proportionately to the amount of time spent in sedentary activities, particularly daily use of the computer. ⁽⁴⁵⁾ This finding has been supported by subsequent cross-sectional survey-based studies in adolescents, ⁽⁴⁴⁾ healthy adults, ⁽²¹⁹⁾ and adults with rheumatoid arthritis. ⁽²³⁰⁾ Holth et al. conducted a survey based examination of the relationship between physical activity and inactivity on prevalence of chronic pain in adults with an 11 year follow-up and found that regular physical activity participation was protective against pain complaints. ⁽²³¹⁾ Others have found contradictory results and reported no relationship between physical activity or sedentary activity and prevalence of pain. ^(46,47) These discrepancies likely result from differences in study design, sample population and definitions of activity and inactivity participation and pain prevalence. For example, the study by Briggs et al. ⁽⁴⁶⁾ included

participants from an Australian birth cohort with a mean age of 14 years, whereas the study by Holth et al. ⁽²³¹⁾ included adults with a mean age of 56 years. Physical activity participation declines as individuals reach adulthood ⁽²³²⁾ and the prevalence of persistent pain conditions increases throughout adolescence and adulthood. ⁽²³³⁾ Pain prevalence was operationalized by Briggs et al. ⁽⁴⁶⁾ as pain in the neck or shoulder region experienced over the lifetime and persistent pain over the last 3 months. However, Holth et al. ⁽²³¹⁾ included pain reported in any part of the body and operationalized pain prevalence as persistent pain lasting longer than 3 months within the past year. Physical activity and sedentary activity in both studies were self-reported; however, participants in Briggs et al. completed nightly reports of daily activity into an electronic diary, while participants in Holth et al. reported usual weekly leisure time exercise participation frequency, duration and intensity.

Although a short-term exacerbation of pain intensity with physical activity is regularly acknowledged, to date the nature of this relationship in youth with JIA has not been described. In addition, studies exploring the short-term temporal relationship between sedentary activity and pain are lacking, and no longitudinal studies on the relationship between activity and inactivity and pain complaints in youth with JIA were found.

2.4.2.1.4 Measurement of physical activity

Caspersen defines physical activity as, “any bodily movement produced by skeletal muscles that results in caloric expenditure.” ⁽²³⁴⁾ However, the measurement of physical activity behaviour has often been conceptualized as voluntary leisure time activity participation, captured by self-report of the intensity, frequency, and mode of activity. ⁽²³⁵⁻²³⁷⁾ Self-reported recalled measures of physical activity have several limitations for field-based activity assessment in youth. Primarily, self-report of activity behaviour is time consuming and intrusive if it is to be frequent enough to be valid and reliable. ⁽²³⁵⁾ Secondly, recall of activity can be biased by social desirability to appear more active, and recalled scores of usual activity participation are prone to over-reporting. ^(238, 239) Third, it is particularly difficult for youth to remember the incidental bouts of activity that occur throughout the day, such as running across the street to catch the bus. ⁽²⁴⁰⁾

Accelerometers provide an unobtrusive method to objectively capture physical activity and inactivity behaviour in youth in real time. ^(235, 241) Accelerometers are small, electronic

devices typically worn on the hip, wrist or ankle that objectively measure the frequency, intensity and duration of physical activity behaviour.⁽²⁴²⁾ Motion or accelerations of the body are captured by movement of a piezoelectric sensor arm within the accelerometer that converts the accelerations of the body collected over a period of time (epoch) into an activity count.⁽²⁴³⁾ A higher count value indicates greater acceleration. Accelerometer counts can be converted into minutes of sedentary, light and moderate to vigorous physical activity using calibration algorithms.⁽²³⁹⁾

Accelerometers have several limitations. Primarily, they are costly devices that must be worn consistently following a prescribed protocol.⁽²⁴³⁾ The Actical accelerometer is not waterproof and therefore could not be worn during water sports or bathing. Activity counts are derived from the acceleration of the body part to which the device is attached, which leads to underestimations of energy expenditure from activities such as cycling when the device is hip mounted since the torso is relatively stationary.⁽²⁴³⁾

2.4.2.2 Emotional affect and mood

Youth with JIA report daily variations in mood⁴ that are related to disease symptoms.^(16, 50) Negative mood correlates with increased daily pain and same day reduced physical activity participation,^(16, 50) indicating a time-varying relationship between the day to day variations in pain and mood.

Russell proposed the Circumplex Model of affect as a parsimonious approach to measuring emotional affect.⁽⁴⁸⁾ In this model positive and negative affect are operationalized as a two dimensional bipolar construct, combining a measure of emotional valence (positive to negative) and a measure of activation or arousal (high activation to low activation). Ekkekakis and Petruzzello presented a four paper series on the utility of the circumplex model for research on affect and exercise in which they concluded that although other models of affect have greater

⁴ Although affect and mood are recognized as distinct constructs, the terms have often been used interchangeably in the research pertaining to pain and mood/affect. For example, Schanberg et al. (2000) use the Facial Affective Scale, a measure of affect, but refer to the construct as “mood.” For the sake of simplicity, and to remain consistent with similar research, the terms will be used interchangeably.

specificity, the circumplex model is parsimonious, easy to administer, and an encompassing, global construct of affect that is very practical in field-based research on exercise. ⁽²⁴⁴⁾

Hall et al. used Russell's Circumplex model to examine the influence of aerobic and anaerobic exercise on emotional affect. ⁽²⁴⁵⁾ In this study of 30 healthy university students, emotional affect was found to improve following the completion of a maximal exercise session. However, throughout the duration of the exercise session, affect was found to steadily deteriorate. Although activation improved during the exercise, emotional valence deteriorated until the session was complete, at which time valence rebounded to a higher level than pre-exercise. Hulley et al. found that affect in healthy children improved with walking to and from school, with a positive relationship between affect and the distance walked. ⁽²⁴⁶⁾ To measure emotional valence, these authors adapted a version of the Feeling Scale of Hardy and Rejeski ⁽²⁴⁷⁾ to create a faces scale with 7 faces; three showing increased grades of positive affect, one neutral face and three showing increased grades of negative affect. To measure activation, they adapted the Felt Arousal Scale of Svebak and Murgatroyd ⁽²⁴⁸⁾ to create a faces scale with six faces. The left anchor face had the words, "Very sleepy" and showed a sleeping face while the right anchor face had the words, "Very awake" and showed a wide awake face.

These studies show an interesting and variable relationship between emotional affect and physical activity. Further investigation is needed to determine if youth with pain conditions experience a similar deterioration and then improvement in mood with maximal exercise. Physical activity may indirectly influence pain through interactions with mood. The within-day variability of mood and the within-day relationship between mood and pain has not been described in youth with JIA. It is critical to note that mood states may directly influence pain by contributing to both systematic and irregular fluctuations in pain intensity.

2.4.3 Summary:

Pain that is persistent seldom stays at a constant intensity throughout the day. Rather, it comes and goes or fluctuates in intensity. Systematic within-day variability in pain has been observed in adults with arthritis with subgroup specific patterns and between-person differences related to pain characteristics such as location of pain and pain sensitivity. To date, systematic variability in pain intensity has not been thoroughly examined in youth with JIA using advanced statistical methods. Alterations in circadian rhythms in physiological functions related to the

HPA axis have been identified as a probable cause of distinct within-day patterns of pain in adults with rheumatoid arthritis, but this has not been explored in youth with JIA. Likewise, the majority of investigation on pain variability has focused on between-person differences with pain being treated as a static variable. Relationships between time-varying factors such as mood have been explored at a daily level, but not at a within-day level. Mood state is an important potential confounding variable in the assessment of systematic within-day variability of pain and the short-term relationship between pain and activity. Although relationships between pain and physical and sedentary activity have been described in cross sectional studies with both healthy and disease populations, the short-term time-varying relationship between activity and pain has not been explored in youth with JIA.

CHAPTER 3

3 THEORETICAL FRAMEWORK

3.1 Modeling Change in Pain Over Time

Modern theoretical constructs of pain perception are unified in the conception of pain as a subjective and individual experience with a diverse array of influences from both the internal and external environments.⁽²⁴⁹⁾ However, from the gate control (GC) theory of Melzack and Wall,⁽²⁵⁰⁾ and numerous biopsychosocial and biobehavioral theories^(26, 251, 252) to the more recent neuromatrix theory of Melzack,⁽²⁵³⁾ the dynamic, time-varying nature of pain has not been explicitly developed in theoretical models.

Conceptualization of changes in pain over time have been limited primarily to those that occur over a period of weeks, months or years as a result of change in disease or injury status or changes in physical, cognitive and emotional development or the aging process.⁽²⁵⁴⁾ This restricted view of change in pain over time leads to the treatment of pain as a static characteristic that varies only with maturation or aging. The frequent use of cross-sectional study designs in pain research and the measurement of pain using single point recalled summary scores attests to the treatment of pain as a static variable.

No theoretical models were found that provided a framework for examining the structure of or interindividual differences in temporal dynamics of pain; therefore, a theoretical model was not available for the development of the study design, or hypothesis building for this research. Deficits of the existing models as a framework for examination of temporal dynamics of pain are outlined in Section 6.5.1. The aims of the research, study design and hypotheses for this research were developed based on the principles and assumptions of chronobiology, which are reviewed in Section 3.2. A purpose of this dissertation is to provide a theoretical model for future studies on pain variability. The GC theory,⁽²⁵⁰⁾ neuromatrix theory,⁽²⁵³⁾ biobehavioral model of pain of McGrath and Hillier⁽²⁶⁾ and Vulnerability-Diathesis-Stress model of Dworkin et al.⁽⁵⁾ are

reviewed because they are foundational to the development of a model for temporal dynamics of pain.

3.1.1 Gate Control Theory

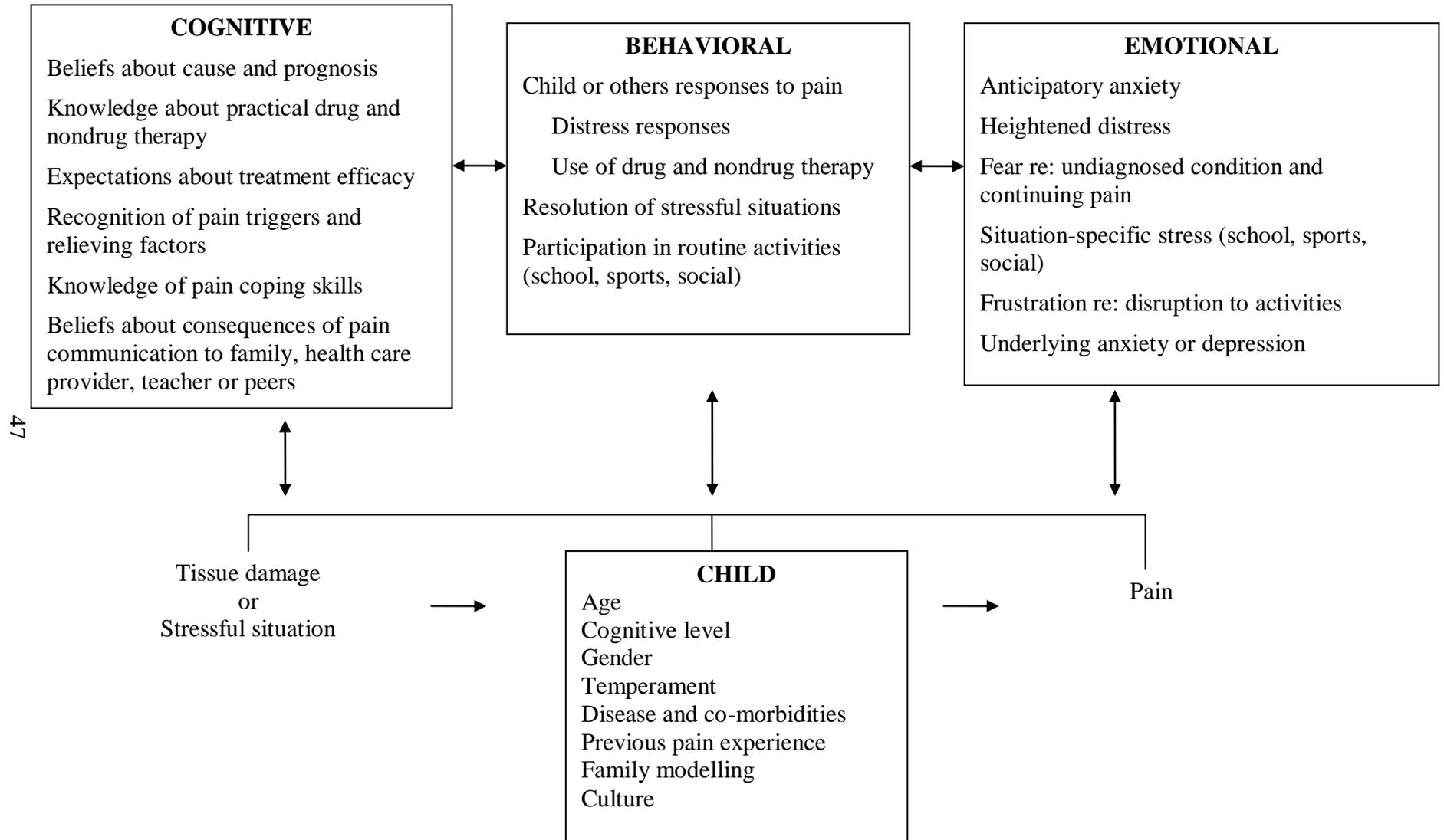
The GC theory proposed by Melzack and Wall in 1965 provided one of the earliest models for the conceptualization of pain as a much more complex process than earlier theories that viewed pain simply as a result of peripheral sensory input, such as the specificity theory of Von Frey, and the pattern theory of Goldschneider, both from the late 1800's. ⁽²⁵⁵⁾ The GC theory presents pain perception as a result of an integration between peripheral stimuli and higher order central nervous system functions: within the dorsal horns of the spinal cord, incoming peripheral stimuli may be altered by other sensations and also by descending excitatory or inhibitory input from higher brain centres. Through these mechanisms, cognitive appraisals or psychological states such as mood and anxiety are thought to have the potential to influence the pain experience. This theory began to explain the differences in pain perception between individuals for similar levels of tissue damage, but it also provided a foundation for pain to be viewed as a dynamic process, influenced by individual trait characteristics as well as internal and external environments that fluctuate over short periods of time. The biopsychosocial and biobehavioral models of illness that followed the GC theory expanded on the range of influential factors. ^(26, 251, 256, 257) Predispositional factors as well as biological, psychological, social and environmental conditions and behavioral responses to pain were thought to contribute to pain onset, persistence and modulation over time.

3.1.2 Biobehavioral Model of McGrath and Hillier

McGrath and Hillier presented a biobehavioral model of children's pain that identified stable person-level characteristics and numerous situational factors that modify pain perception (Figure 3-1). ⁽²⁶⁾ McGrath and Hillier acknowledge that fluctuations in cognitive, behavioral and emotional situational factors have the potential to trigger, intensify or prolong pain episodes and modify disability related to the pain experience in children. They also point to situational factors as primary therapeutic targets and stress the importance of recognizing which situational factors are relevant to each individual child.

Figure 3-1: Situational and child factors that modify pain and disability

Adapted with permission from P.A. McGrath²⁶



3.1.3 Neuromatrix Theory

Melzack's neuromatrix theory reconceptualized pain from a peripheral sensory input modulated by the central nervous system, to that of an output of a complex neural network, the neuromatrix. The neuromatrix is thought to regulate a genetically programmed sense of the body, or "body-self," throughout a wide distribution of centres across the brain. Sensory inputs from the periphery are processed and integrated across the neuromatrix and if this input deviates from what is perceived as the normal body-self, characteristic neurosignature outputs, such as pain, may be triggered. The neuromatrix also activates neural and hormonal programs and behavioral activities in response to peripheral input and in parallel with neurosignatures.^(253, 258) This is perhaps the most revolutionary aspect of the neuromatrix theory: the concept of pain as an output. From this perspective, pain can be viewed as a noxious motivator for behavioral change or as a feedback or feedforward mechanism designed to return the body to a state of homeostasis.⁽²⁵⁸⁾ This is a particularly effective protective defense against harm in an acute pain situation where pain truly signals real or potential tissue damage, but not in a chronic pain situation where pain is maintained in the absence of a noxious stimulus or obvious need for behavior change.⁽²⁵⁸⁾

The neuromatrix theory adds to previous models by recognizing that pain neurosignatures can occur in the absence of peripheral input, but also that the neuromatrix, the sense of body-self and neurosignatures are genetically programmed yet modified by sensory experiences across the life-span. This theory is supported by the work of Dworkin et al.,⁽⁵⁾ Kerns et al.⁽²⁵⁶⁾ and Flor et al.^(259, 260) who identified vulnerabilities that predispose individuals to the development of persistent pain conditions.

3.1.4 Vulnerability Diathesis Stress Model

Dworkin et al. proposed the Vulnerability Diathesis Stress (VDS) model to explain the development of persistent pain conditions in adults. In this model they identify stable biological, psychological and social factors that precede the onset of pain and create a vulnerability continuum that predisposes an individual to the development of persistent pain. They identified biological vulnerabilities such as genetic factors, or changes in physiology or structure as a result of prior disease or injury (e.g. sympathetic reactivity, scoliosis, central sensitization).

Psychological vulnerabilities identified included personality traits affecting pain such as somatization and hypervigilance, psychopathologies such as depression or substance abuse disorders, or exposure to traumatic events such as sexual or physical abuse.

Not all individuals at risk of developing persistent pain conditions do so; however, in the presence of a diathesis (an illness or injury that causes a painful episode; e.g. arthritis), an individual already at risk is placed at further risk of development of persistent pain. Most individuals identify the diathesis as the cause of their persistent pain as this is the injury or illness that would be most easily identified as a precipitating or causal event. The predisposing factors and diathesis alone are necessary, but may not be sufficient to create a persistent pain condition. Dworkin et al. propose that individuals that experience a higher degree of psychological stress in the months immediately preceding the diathesis will be most likely to develop a persistent pain condition. Similar to the vulnerability factors, both the diathesis and the level of psychological stress exert a continuum of severity of influence on the individual's risk level.

3.1.5 Summary

McGrath and Hillier's biobehavioral model and the neuromatrix theory specify situational (phasic) factors as potential modifiers of the pain experience. The Vulnerability Diathesis Stress model of Dworkin et al. provides a framework to examine the individual differences in predisposition to development of persistent pain. The Vulnerability Perturbation model of pain will be presented in Chapter 6 in light of the research findings presented in Chapter 5 and in consideration of the literature review and theoretical foundations discussed in Chapters 2 and 3. This model will extend the models of McGrath and Hillier and Dworkin et al. to provide a framework for the examination of temporal dynamics of pain.

3.2 Principles of Chronobiology

Development of the aims and questions for this research were guided by the principles of chronobiology. Chronobiology is the term used to refer to the study of temporal characteristics of biological phenomena. ⁽³⁾ The majority of biological functions vary in repeating patterns over time with characteristic period lengths. ⁽¹⁶⁰⁾ Many physiological and endocrine functions that affect nociception show circadian rhythms. ^(3, 183) Literature on the chronobiology of pain was outlined in Sections 2.3 and 2.4.

3.2.1 Biological Clock

Since the mid 1960's the existence of an internal regulator of biological rhythms has been acknowledged. ⁽³⁾ This master "biological clock" has been identified as the suprachiasmatic nucleus (SCN) located in the hypothalamus of the brain in mammals. The SCN is genetically programmed to synchronize biological rhythms within the body that drive physiological, endocrine and behavioural processes towards the goal of maintaining homeostasis. ⁽²⁶¹⁾ Genetic manipulations of the SCN result in altered rhythmicity of some biological functions. ⁽¹⁶⁰⁾

Even in the absence of environmental temporal cues, many physiological and endocrine functions vary in a 24 hour period and are therefore called *circadian* rhythms from the Latin words "*circa*," meaning "close to" and "*dies*" meaning "day." ⁽¹⁶⁰⁾ Behavioural cues such as the sleep-wake cycle, food intake and physical activity-inactivity patterns as well as environmental cues such as the light-dark cycle entrain the SCN to regulate biological rhythms that are synchronized with the external environment. The light-dark cycle appears to be the most important environmental synchronizer of the SCN. ⁽¹⁶⁷⁾

3.2.2 Describing Rhythm Characteristics

Chronobiology is aimed at describing and explaining the temporal characteristics of rhythms. ⁽⁶²⁾ Rhythms are described by their period, amplitude, and phase. The rhythm period is the time required to complete one cycle. There are three main period categories of biological rhythms: ultradian (<20 hours), circadian (approximately 24 hours) and infradian (>28 hours). The amplitude is the numeric distance between the mean level of the rhythm to the peak or trough of the mathematical model used to describe the rhythm, usually a cosine curve. ⁽³⁾ Amplitude is a measure of the variability of the biological function. A rhythm phase is a definable point in the repeating cycle of the rhythm. For example, the peak (acrophase) and trough (bathypase) of the rhythm are identifiable through mathematical modelling.

Data collection for rhythm analysis is constrained by the nature of the variable of interest, finances, time and ethical considerations. ^(62, 160) For example, measurement of a self-reported variable during the sleep-hours is not reasonable. More frequent sampling provides greater detail of the rhythm and more confidence in the estimates of the rhythm parameters; however, it is more expensive for collection and analysis of biological samples and more burdensome to

participants for self-reported variables. Redfern et al. compared four sampling frequencies for cortisol and demonstrated that when comparing sampling every 30 minutes to sampling every 4 hours, even with the least frequent sampling density, general rhythm characteristics could still be identified, but the number of peaks observed during the day, the size of the peaks and their timing could only be approximated. ⁽¹⁶⁷⁾

3.2.3 Development of Research Aims and Questions

The assumptions of chronobiology are that there are genetically determined, endogenously driven bases for biological rhythms that are stable under synchronized living conditions. However, the pattern of the rhythm may be altered or masked by changes in the environment. ^(3, 160) This research had two aims that were developed in light of the assumptions of chronobiology. Pain intensity data were examined for possible circadian (24 hour) rhythms on the assumption that endogenously driven physiological processes that affect nociception and the underlying circadian variability in pain sensitivity would result in systematic variability in pain intensity for youth with JIA. The short-term relationships between physical activity and pain and mood and pain were examined to determine if changes in these variables were associated with irregular fluctuations in pain intensity. A more complex chronobiological analysis involving isolation of the biological rhythms influencing systematic variations in pain and identification of overlapping rhythms of higher frequencies was not within the scope of this research as this would require a desynchronization protocol and measurement of pain throughout the sleep hours.

3.3 Research Assumptions

The following assumptions were taken with this research:

1. Construct validity of a pain intensity measure is independent of the type of hand held device on which the measure is conducted, leading to the assumption that changes in pain intensity can be captured by self-report using an electronic diary for the iPod Touch. This assumption is based on the findings from several studies on pain in children using different electronic devices that reported similar pain intensity reports between paper and electronic diaries ⁽⁵⁵⁾, adequate construct validity between related measures of pain ⁽¹⁹⁾ and relationships between daily stressors and pain occurrence. ⁽¹²⁴⁾

2. A 24 hour period is assumed to be the most appropriate cycle for the cosinor analysis of systematic fluctuations in pain in childhood arthritis. This assumption is based on the literature demonstrating statistically significant 24 hour cosine rhythms in pain in adults with arthritis. In addition, biologically important variables for nociception, such as cortisol and IL-6, have predictable 24 hour circadian rhythms, and environmental synchronizers such as sleep-wake and activity-rest cycles generally follow a 24 hour pattern.
3. Pain in childhood arthritis will show one peak and one trough during a 24 hour cycle. Sampling three to seven times per day is sufficient to observe the ascending and descending portions of the cosine curve. This assumption is based on the adult arthritis cosinor analysis literature which shows significant 24 hour cosine variability.^(27, 30, 142, 144, 147) The literature does not provide guidance as to an optimal number of data points per day for observation of this rhythm.
4. Four days of sampling are adequate to capture the range of physical activity behaviors in youth regardless of whether days of observation include weekend-days. This assumption is based on the recommendations of Trost et al.⁽²⁴²⁾ for a minimum of four days of monitoring to capture physical activity behaviours in youth. The current study is not concerned with quantifying each child's typical activity behaviours, rather that the range of behaviours is captured throughout the four day observation period.
5. Cut-points used to convert a continuous measure of pain into an ordinal category are valid boundaries for distinguishing mild from moderate and moderate from severe pain. Categorization of pain scores is described in Section 4.1.4.3.1.
6. Combining minutes of physical activity and minutes of sedentariness into an ordinal categorization of physical activity based on sample quartiles is a valid representation of the range of physical activity behaviours. Categorization of physical activity is described in Section 5.2.8.
7. The relationship between pain and physical activity can be captured with a pain sampling frequency of seven times per day and by summarizing activity across two hour windows.

CHAPTER 4

4 METHODOLOGY

This chapter provides a detailed description of the research design, sampling methods, study procedures, ethical considerations and statistical analysis methods used in Study 1 and Study 2. Methods of analysis for both studies are summarized in Appendix B.

4.1 Study 1

4.1.1 Research Design

Study 1 was an analysis of data collected by Stinson et al. from two prospective observational studies on the construct validity of an electronic diary.⁽¹⁹⁾ In these studies, youth were invited to participate if they were diagnosed by a pediatric rheumatologist with active JIA according to the ILAR criteria,⁽⁷⁾ were between the ages of 9 and 18, able to speak and read English, and attended one of two university affiliated pediatric rheumatology clinics in Toronto, Ontario between January and December, 2005. Youth in Stinson's second study had an additional criterion of being scheduled to receive an intra-articular steroid joint injection. Youth were ineligible for enrolment if they had a known major cognitive or psychiatric disorder, visual problems, or hand deformities that would interfere with their ability to use the electronic diary, or other known major painful medical disorders. Seventy-six adolescents were recruited for Stinson's first study, and 36 were recruited for the second study. In Stinson's first study, participants completed a multidimensional pain survey on an electronic diary (e-Ouch)⁽²⁶²⁾ three times daily for two weeks; on waking, after school and before bedtime. In the second study, participants were scheduled to receive intra-articular steroid joint injections. Participants from the second study completed the same pain survey three times daily for three weeks beginning one week prior to the scheduled joint injection, and continuing for two weeks following the joint injection. Study procedures have been previously described in greater detail.⁽¹⁹⁾ Demographic

and questionnaire response data from each participant used in reanalysis for the present Study 1 included: age, sex, diagnosis (JIA subtype), disease duration (years), disease severity (PGADS), and total number of active joints.

4.1.2 Data Sampling

For Study 1, pain intensity data from the two studies by Stinson et al. ⁽¹⁹⁾ were analyzed to explore the data for systematic variability of pain intensity. Data from a total of 112 participants were available for analysis. Only the first week of data was used from both studies to eliminate any potential confounding resulting from the intra-articular joint injections received by participants before the second week in Stinson's second study and because there were fewer missing data in the first week compared to following weeks. ⁽¹⁹⁾ Therefore, each participant provided a single time-series of repeated measures of pain intensity data with up to 21 time points (three times per day for seven days).

4.1.3 Measures

Pain Intensity: A question on pain intensity was part of the multidimensional survey on the e-Ouch electronic diary programmed onto a stylus driven portable personal digital assistant (PDA). ⁽²⁶²⁾ The pain intensity question was worded, "Touch the mark and move it to show how much PAIN or HURT you have right now." Participants recorded a response on a 5 cm sliding VAS with the anchors "no pain" at the far left and "very much pain" at the far right. The usability and construct validity of the VAS measured with an electronic diary have been described previously. ^(19,110, 149) The VAS for measuring pain intensity using an electronic diary has demonstrated high test-retest reliability in adults with upper extremity injuries (ICC = 0.96). ⁽²⁶³⁾ Output for the question was delivered electronically to a server web-page in the form of a 0 to 100 continuous scale with 0 indicating "no pain" and 100 indicating "very much pain." Pain intensity was the only question from the e-Ouch diary included in the analysis for this study.

Age: Age was measured in years and obtained from participant's clinical records.

Physician Global Assessment of Disease Severity (PGADS): PGADS was assessed by the participant's pediatric rheumatologist on clinical examination, scored on a 10 cm VAS with anchors of "0 = no activity" on the left and "10 = maximum activity" on the right. PGADS was

recorded to one decimal point. PGADS has demonstrated good construct validity, inter-rater reliability (ICC range = 0.83 to 0.90)⁽²⁶⁴⁾ and responsiveness to change in disease status (Standardized response median = 1.33).⁽²⁶⁵⁻²⁶⁷⁾

Disease Duration: Disease duration was obtained from participant's clinical records and was recorded in years to one decimal point.

Total Number of Active Joints: Total number of active joints was assessed by the participant's pediatric rheumatologist on clinical examination.

JIA Subtype: The subtype of JIA was obtained from participant's clinical records, determined by the pediatric rheumatologist according to the ILAR criteria (See Appendix A for JIA Subtype Classifications).⁽⁷⁾

4.1.4 Analytic Procedures

4.1.4.1 Distribution and imputations

Measures of dispersion were analyzed for the demographic and disease characteristics of the sample as well as pain intensity characteristics for the total sample and for individual cases. Individual means for each time of day (morning, afternoon, evening) were calculated. Balanced datasets were required to conduct the single cosinor procedure on the individual time-series. Two imputation methods were compared on measures of dispersion (mean, standard deviation) to determine which method produced a balanced dataset that best represented the original non-imputed dataset. For the first method, missing data were imputed with individual time of day means. For example, if a participant was missing the afternoon pain score of day 2, the mean afternoon pain score calculated from the remaining afternoon pain scores for that individual was computed and imputed for the missing value. This deterministic method of imputation was chosen in order to retain any potential structure in the time series without removing potential uncertainty about the structure.^(268, 269) For the second method, random imputations based on the individual's range of pain scores were computed using a web-based random number generator (www.random.org). Also, outcomes of the cosinor analysis were compared between the full dataset, a dataset containing only those participants with at least 6 days of full data and a data set containing participants with at least 5 days of full data to determine the effect of missingness on the proportion of significant cosinor analyses.

4.1.4.2 Two stage regression - cosinor analysis and logistic regression

For the first stage of the two stage regression procedure, each individual time series was analyzed using the single cosinor procedure (Objectives 1.1).⁽¹⁾ Parameter estimates obtained from these analyses were used for the second stage of analysis (Objectives 1.2). Retained parameter estimates included the mesor, amplitude, acrophase, and p-value from the zero-amplitude test. Cosinor procedure statistical analyses were performed on MATLAB software (R2009a, The MathWorks Inc., Natick, MA, www.mathworks.com). Existing code published on MATLAB Central⁽²⁷⁰⁾ was modified to conduct the cosinor analysis on the 21 point time series. The second stage of analysis consisted of a forward stepwise logistic regression. The outcome variable was significance ($p \leq 0.05$) of the zero amplitude test on cosinor analysis. The following steps outlined by Kleinbaum et al.⁽¹⁵³⁾ were used to build the logistic regression model.

1. Univariate analysis: variables that have a p value ≤ 0.25 on univariate analysis are retained for multiple regression analysis.
2. Biologically relevant variables are retained for multiple regression analysis even if the p value on univariate analysis exceeds 0.25.
3. Multiple regression analysis: variables with a p value ≤ 0.05 are retained as main effects in the full model.
4. Interactions are tested separately within the full model and retained in the final model if $p < 0.05$. Interactions selected for testing are based on theory.

4.1.4.2.1 Cosinor analysis on Monte Carlo simulated data

To determine if the proportion of time-series meeting significance was greater than that found by chance alone, a Monte Carlo simulation procedure was conducted using resampled data to simulate 1000 equivalent matrices of 85 cases with 21 time points. Code was written for MATLAB to produce matrices from the 85 time-series in the dataset. Matrices were produced by randomly selecting cases by ID number (with replacement) then randomly selecting 21 pain scores (with replacement). The single cosinor procedure was performed on the simulated time-series from the 1000 matrices (85000 time series) using MATLAB code written specifically for this purpose. The proportion of significant cosinor procedures for each simulated matrix was reported which provided a range of proportions that would occur by chance alone that could then

be compared with the proportion of significant cosinor procedures produced from the original clinical data.

4.1.4.3 Generalized estimating equations

GEEs were computed to examine the data for time of day effect (Objective 1.3). These were conducted on raw data without imputations. Pain, as the dependent variable, was categorized as an ordinal categorical variable (categories are described in the following section). Demographic and disease variables were included as time-invariant predictors. Time of day was the only time-varying predictor variable. Model building strategies were based on Kleinbaum and Kupper and will be discussed in the results section. ^(153, 180)

4.1.4.3.1 Categorization of pain scores

Since the pain intensity data were not normally distributed, pain scores from the VAS were converted to a categorical outcome with four categories. Although there are no definitive cut-points for pain categories derived from VAS scores, several authors have attempted to correlate patient's verbal categorical ratings of pain with VAS or numeric rating scores (NRS). Hanley et al. found that there was generally good agreement between individuals with spinal cord injury and chronic pain as to which category most numbers on the NRS should belong; however there was disagreement on the upper boundaries of the mild and moderate categories. ⁽²⁷¹⁾ Different authors have assigned the number 4 on a 0 to 10 NRS scale to either the mild ⁽²⁷²⁻²⁷⁴⁾ or moderate category ⁽²⁷⁵⁻²⁷⁷⁾ and the number 7 to either the moderate ⁽²⁷¹⁾ or severe ⁽²⁷¹⁻²⁷⁴⁾ categories. To test the validity of the pain categorization, analyses were run using two sets of categorization cut-points (Table 4.1). If differences in parameter estimates did not differ more than 20 percent on GEE analysis between the two categorization strategies, the cut-points that provided the most balanced frequencies in each category would be selected as the final strategy. If differences in parameter estimates did differ more than 20 percent, Strategy 2 would be used since these are most similar to cut-points described in the literature. The cut-points used in Study 1 would be selected for Study 2.

Table 4-1: Cut-points for two pain categorization strategies

Pain Category	VAS Scores for Categorization 1	VAS Scores for Categorization 2
No Pain	0	0
Mild	1-30	1-30
Moderate	31-60	31-69
Severe	61-100	70-100

4.1.5 Ethical Considerations

University of Saskatchewan (U of S) behavioral research board ethics approval was obtained for analysis of the data. Data transmitted from Dr. Stinson were de-identified. Participant names, addresses and phone numbers were not transmitted. All data were treated with confidentiality during the secondary analysis. Raw data were stored in a locked filing cabinet and on a pass-word protected computer file in the investigator's office. Study reports contained no identifying information.

4.2 Study 2

4.2.1 Research Design

Study 2 was a prospective observational study design to describe and explain the within-day variability of pain intensity in youth with JIA and non-arthritic pain conditions and to examine the short-term relationship between pain intensity and physical activity. The data available and results of Study 1 informed the design and analysis of Study 2. This is described in Section 4.2.6.

4.2.2 Setting

Participants were recruited from the pediatric rheumatology clinic at the Royal University Hospital, Saskatoon, Saskatchewan, Canada. Two pediatric rheumatologists practice from this

clinic, which serves the entire provincial population. Data collection took place in the participants' usual environment.

4.2.3 Sample

4.2.3.1 Sampling procedure and participants

A convenience sample was drawn from the clinical case-load of two pediatric rheumatologists in the single clinic. Eligible participants were invited to enrol until a sufficient sample was obtained. There were two groups of participants: JIA and non-JIA. General eligibility criteria for both groups included:

- a) youth between the ages of 8 and 18 years attending the pediatric rheumatology clinic at Royal University Hospital, Saskatoon, SK, Canada
- b) participants and parent/guardian able to speak and read in English
- c) independently ambulatory without aides
- d) experienced pain attributed to the condition and self-reported pain related to the condition in the past week
- e) live within a 2 hour driving radius of Saskatoon, SK
- f) no known cognitive, psychiatric, visual or motor impairments that would impede self-report of pain or use of the electronic diary
- g) available to complete the study procedures for four consecutive days

Additional inclusion criteria for the JIA group were that they be diagnosed with JIA by a pediatric rheumatologist according to the ILAR criteria. ⁽⁷⁾ Additional inclusion criteria for the non-JIA group were that they have a pain condition not meeting JIA diagnostic criteria including, but not limited to, recurrent or persistent back or neck pain, lower extremity pain, upper extremity pain, headaches, abdominal pain, or wide-spread pain (e.g. fibromyalgia).

4.2.3.2 Sampling duration and sample size

Data were collected over four days for two primary reasons. First, Nelson ⁽¹⁾ recommends at least two full cycles of a rhythm to satisfy the requirement of the cosinor analysis. A 24 hour cycle was examined; therefore, a minimum of two days of data were required for cosinor analysis. Trost et al. ⁽²⁴²⁾ recommends no less than four days of activity monitoring with

accelerometers in order to obtain an accurate representation of physical activity behaviour in children. Therefore, data were collected over four days in order to meet the requirements of cosinor analysis and to provide a sufficient physical activity sample to capture a range of physical activity behaviours. The study protocol was not extended beyond four days in order to minimize participant burden.

Cosinor analyses were conducted on simulated matrixes derived from Monte Carlo bootstrapping sampling of the original datasets in order to determine if the proportion of cosinor analyses found in the clinical sample exceeded that which would be found by chance alone (Objectives 1.1 and 2.1). These procedures are described in section 4.1.4.2.1 (Study 1) and 4.2.6.2 (Study 2).

Sample size necessary for logistic regression of the probability of having a significant zero-amplitude test on cosinor analysis ($Y=1$) was calculated based on the binary independent variable of sex (Objective 1.2). A sample size of 90 participants (of which 70% are in the group sex=female and 30% are in the group sex=male) achieves 83% power at a 0.050 significance level to detect a change in the probability of ($Y=1$) from the baseline chance value of 0.05 to the probability of $Y=1$ at 0.30.⁽²⁷⁸⁾ A sample size of 80 participants would achieve 79% power under the same criteria. Therefore, Study 1 requires a sample size greater than 80 participants to sufficiently power the logistic regression if the proportion of significant zero-amplitude tests in the clinical sample is approximately 30%. In the adult literature, the proportion of significant zero-amplitude tests ranged from 40 to 100%.^(27, 30, 142, 144, 147, 169)

Due to the limited number of participants available for recruitment for Study 2, it was acknowledged that the logistic regression for Study 2 would be underpowered to detect a change in the probability of $Y=1$ from the baseline. Therefore, findings from the logistic regression were interpreted by examination of the width of the confidence intervals to examine precision of results (Objective 2.2).⁽²⁷⁹⁾

Sufficient data for GEE analysis depends on the numbers of clusters (participants), observations per cluster and levels of both the observation and each variable. In order to avoid errors with the estimates, Stokes et al. recommend 5 observations per level of the dependent variable and per level of the independent variables in the model.⁽¹⁸⁰⁾ With four ordinal levels of

pain as the dependent variable, a model containing over 88 variable levels (e.g. 22 categorical variables with 4 levels each) could be fit for Study 1 GEE analysis since 21 observations were collected from 85 participants (Objective 1.3). For study 2, if a total of 30 participants were recruited, a model containing over 42 variable levels (e.g. 10 categorical variables with 4 levels each) could be fit for Study 2 GEE analysis if data from both groups were combined since 28 observations per participant were collected (Objective 2.3).⁽¹⁸⁰⁾ The goal of enrolment was to recruit 15 participants into both the JIA and non-JIA groups. Assuming attrition of 2 participants from each group, this would provide sufficient data to enable examination of main effects and multiple interactions if data from the JIA and non-JIA groups are combined. This amount of data would be sufficient for separate group (JIA and non-JIA) GEE analysis with models containing up to 18 variable levels (e.g. 6 categorical variables with 3 levels each) which would enable examination of main effects only.

4.2.4 Study Procedures

4.2.4.1 Recruitment procedures

Clinical registries were screened for eligible participants by a research nurse. Recruitment letters (Appendix C) were mailed to eligible participants one month preceding a forthcoming clinical appointment with the standard appointment reminder letter. In the letter, interested participants or their care-givers were asked to contact the investigator by phone or email to arrange an appointment to enrol. Eligible participants were also approached following clinical appointments by a research nurse not involved in clinical care to enquire about their interest in participating in the study. The investigator was available on clinic days to explain the study and determine eligibility for those interested in participating. Enrolment appointments were arranged at a convenient time and location for the participants. Data collection began within three days following the enrolment appointment on a day that was convenient for participants to begin data collection.

4.2.4.2 Study procedure overview

Data collection for the study took place over four consecutive days. Participants were asked to self-report pain, mood and related symptoms seven times per day over the four days on

an electronic diary developed for the study. Participants wore an accelerometer continuously during the four days. Saliva samples were collected twice per day for the four days; immediately on waking and just before going to bed in the evening. There were four paper questionnaires; two for parents/guardians and two for participants. Anthropometric data were collected in the clinic at enrollment.

4.2.4.3 Enrolment and training

4.2.4.3.1 Electronic diary - PInGo app for the iPod Touch

Youth and their care-givers who indicated an interest in participating in the study met with the investigator to obtain consent and assent (Appendices D and E), learn about the study procedures, be screened for the ability to self-report pain on an electronic diary, practice using the electronic diary, be equipped with the accelerometer, learn about saliva sample procedures and obtain the four study questionnaires. Study information was also provided on a take-home study protocol instruction sheet (Appendix F).

This meeting took place either in a room in the clinic, or at a private location that was convenient for participants, such as the participant's home. Once consent was obtained, participants were provided a unique identification (ID) number. After explaining the general procedures, participants were given a brief explanation about the PInGo electronic diary application (app) on the iPod Touch (Apple, Inc.). Participants were given basic instructions on how to turn on and off the iPod, how to check if the unit needed recharging, how to recharge, how to access the PInGo app, when the signal prompts would alarm, how to complete the app, and time-out features of the app. This information was provided verbally by the investigator with a take-home general iPod information sheet. Participants were then given training on using the PInGo app following a standardized practice vignette that was also used to screen for the ability to self-report pain and report appropriate gradations and directions of change in measured variables (Appendix G). The vignette was used as participants worked through the practice app with supervision from the investigator. The vignette required participants to report various levels of pain intensity, pain unpleasantness and interference and demonstrate the ability to modify reports in the expected direction and expected magnitude based on the vignette information. The practice session was used to screen participants' ability to use the iPod and to understand the

PInGo questions. Immediate feedback was provided to participants if questions arose. Participants were informed that they could not move forward from one question to the next on the app unless an answer was provided. Participants were also informed that they could not move backwards to previous questions on the app. During the training, participants were encouraged to think carefully about their answers to each question in order to avoid input errors. Participants were asked to complete the PInGo app without assistance or interaction with parents or any other individual.

Participants were then provided with an iPod downloaded with the PInGo app. Each iPod had a unique user number that was kept on file by the investigator to link data transferred from the iPod to the participant's ID number. Participants selected a carrying case for the iPod from a range of options. The carrying cases were equipped with a carabiner clip that could be attached to a belt or belt loop. Participants were asked to keep the iPod with them at all times unless they felt that it was not safe to carry, for example, during Physical Education class or sporting events. Participants were asked to leave the iPod with a responsible adult if they were not able to keep it with them. Participants were provided a recharging cable for the iPod and informed that assistance from the investigator was available at any time during the study period by telephone or email. Participants were asked to contact the investigator immediately if the iPod was lost, broken or stolen and a replacement unit would be provided as soon as possible. Participants and their families were informed that they were not financially responsible for loss or damage to the iPod should that occur.

Data from the PInGo app were sent automatically, when a network connection was made, to a password protected web-page on a server web-page built specifically for this study. All data were identity linked for confidentiality, meaning that transmitted data were coded with only the iPod user identification number. Only the investigator had access to the log that linked the participant's ID number to the iPod user number. Data were collected in comma delimited format with questions identified by number.

The iPods were programmed to signal prompt participants to complete the survey seven times per day at 8:00 am, 10:00 am, 12:00 pm, 2:00 pm, 4:00 pm, 6:00 pm, and 8:00 pm. These times were selected for several reasons. First, this schedule was based on times that would be minimally disruptive to the youth's normal routine during both week days and weekends for

children and adolescents ranging from 8 to 17 years old. This sampling density had sufficient data points to observe 24 hour frequencies of systematic variability in pain intensity and more frequent cycle periods, should they exist. This frequency also minimized the intrusiveness of the survey on school times. Only the 10:00 am and 2:00 pm surveys would potentially interrupt class-room times on school days. Letters explaining the purpose and protocol of the study were provided to students to give to teachers and school administration if data collection took place during school times (Appendix H). In this letter, school personnel were invited to contact the investigator if more information about the study was required. Participants were informed that no confidential information would be shared with teachers or school staff if the investigator was contacted. Participants were asked to follow the teacher's instructions regarding data collection during school times; therefore, if a teacher did not want the student to complete the survey or wear the accelerometer during school times, the participant was to comply with the teacher's instruction and contact the study investigator by telephone or email to determine if rescheduling of data collection was required.

4.2.4.3.2 Anthropometric data

At the clinic visit, the following anthropometric data were collected by the investigator: body weight, standing height and sitting height. Anthropometric data were used to calibrate the accelerometer for each participant and to calculate PHV that was used as a measure of maturation. ⁽²⁸⁰⁾

4.2.4.3.3 Accelerometer

Participants wore Actical (Mini Mitter Co, Inc, Bend, OR) accelerometers continuously over the four day study period, removing them only to avoid submersing them in water in a bath, shower or when swimming. Participants were instructed that they were allowed to remove the accelerometer at night if it was uncomfortable or interfered with sleep. Participants were also asked to use judgement and remove the accelerometer during activities in which wearing the belt or accelerometer might cause them harm. Participants were asked to keep track of the times that the accelerometer was removed and reason for removal on a paper log (Appendix I).

4.2.4.3.4 Cortisol

Saliva collection followed a recommended protocol for research with children.^(281, 282) Participants were provided eight Salivette tubes (Salimetrics, Pennsylvania, USA) to collect saliva samples which were used to measure cortisol. Salivette tubes consist of an outer plastic tube body and saliva receptacle, a suspension tube with an outlet at the bottom for filtration of saliva during centrifugation, a cotton swab for collection of the saliva sample and a tube cap.

The procedure for collecting saliva was demonstrated to participants during the enrolment visit and also provided in written instructions (Appendix F). During the enrolment visit, participants were given the opportunity to handle a sample tube and practice opening and closing the correct chamber. Participants were instructed to avoid caffeinated foods and beverages for two hours prior to collecting saliva, and to avoid all food and drink for 20 minutes prior to collection. Salivette tubes had a single label with the participant ID number, the word "Morning" or "Evening," and the day number to identify the order in which the samples were to be provided. For example, the first tube for participant A01 was labelled, "A01 Morning 1," the second tube was labelled, "A01 Evening 1," the third tube was labelled, "A01 Morning 2," and so on. The label also had a blank line for the investigator to fill in the date of sample collection and for participants to fill in the time of day that the sample was collected.

Participants were asked to provide samples only at the times instructed and to leave empty any tubes that were missed. Participants were encouraged to place the morning Salivette tube on a bed-side table or in a visible location that would prompt them to provide the sample first thing in the morning. Participants were asked to collect the morning sample as soon as they woke up, before eating or brushing their teeth and to collect the evening sample just before they went to bed at night. The Salivette tubes were provided in a medium sized zippered freezer storage bag. Participants and their care givers were instructed to store all used and unused tubes in the same storage bag in the freezer to avoid misplacement. Salivary cortisol is a robust compound that is stable either frozen or at room temperature for several days as well as when frozen, thawed and refrozen.⁽²⁸³⁾

4.2.4.3.5 Questionnaires

Participants were provided a questionnaire package which could be completed during the appointment or at home and returned with the study equipment. Two questionnaires were for a parent or guardian to complete and two were for the participant to complete (questionnaires are described in Section 4.2.5.2).

4.2.4.3.6 Equipment collection

At the enrolment visit, the investigator arranged with the parent or guardian a time and location to collect the cortisol samples, iPod and accessories, accelerometer, and questionnaires. Participants from outside of the city of Saskatoon, SK were given the option of returning the samples and equipment by bus or courier. If this option was chosen, participants were given appropriate packaging and instructions and were asked to contact the investigator when the samples and equipment were sent. Equipment was sent collect so participants did not have to pay for delivery.

4.2.4.3.7 Clinical data

With consent, the participant's chart was reviewed by a research nurse for date of disease onset, diagnosis or subtype of JIA, and the ESR obtained from the most recent blood work. ESR is a nonspecific measure of inflammation.⁽⁸⁰⁾ A normal value for children and adolescents with arthritis is <20mm/hour.⁽²⁸⁴⁾ Data was collected using a standardized collection form (Appendix J).

4.2.4.3.8 Participants and refusals

The research nurse kept a log of the number of youth attending clinic during the recruitment period, numbers of ineligible youth and reasons for ineligibility, numbers eligible for recruitment and approached to participate, number of refusals and reasons for refusal.

4.2.4.3.9 Compensation

Participants were verbally encouraged during the enrolment and training to complete every possible diary entry. To encourage full participation and return of equipment, questionnaires and saliva tubes, participants were informed that they would receive a gift card

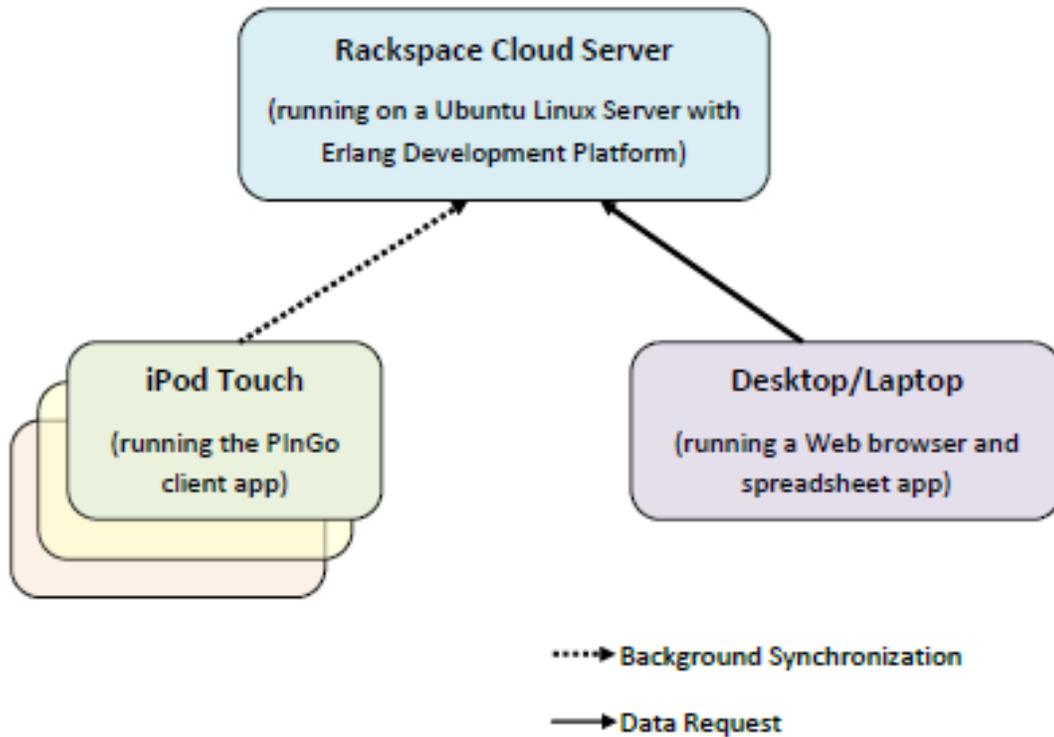
from a vendor of their choice once equipment was received by the investigator. Participants were given one dollar for every diary entry that was completed and an extra two dollars for completion of the paper questionnaires, with a total possible compensation of \$30 over the four days. Once the data were examined for completeness, the gift card was mailed to participants with a thank you letter indicating that their participation in the study was complete (Appendix K).

4.2.5 Measurement instruments

4.2.5.1 PInGo electronic diary

The Pain Information on the Go (PInGo) system architecture consisted of a client application (app) to run on the iPod Touch and a server. The PInGo app and server were developed by programmers at the University of Saskatchewan Department of Computer Sciences on specifications provided by the study investigator (Figure 4-1). Data collected by the iPod app were automatically sent in the background to a Rackspace Cloud Server (www.Rackspace.com) once a network connection was made, so the participant did not have to manually submit data. Once the equipment was returned to the study investigator, the iPod was connected to the network. A Web browser on a desktop was used to retrieve secured data collected from the server and imported into a spreadsheet. PInGo app questions and format were based on the e-Touch diary ⁽²⁶²⁾ with modifications for the purpose of the current research.

Figure 4-1: PInGo Architecture



The PInGo app was 16 pages (screens) long following the opening page from which participants entered the survey. Three sets of questions were developed that differed by only three pages. The first morning survey and last survey of the day included prompts to provide the saliva sample, and there were minor differences in the interference questions between each set of questions. The surveys were only accessible for one hour following the scheduled time of data collection. This limited response window balanced the need for flexibility with the need to restrict survey collection to narrow time blocks in order to simplify final analysis for assessment of correlation between pain and physical activity. The "morning" survey was accessible to participants during a 60 minute window from 8:00 am to 9:00 am. The "afternoon" surveys were accessible for 60 minute windows at 10:00, 12:00, 2:00, 4:00 and 6:00, and the "evening" survey was accessible from 8:00 pm to 9:00 pm. The questions included in the morning PInGo app are outlined below in order to identify differences between the PInGo and e-Ouch questions and to identify and justify modifications. The afternoon and evening survey questions are outlined in Appendix L. Only measures used in the analysis are reviewed for reliability and validity.

Page 1

Purpose: Prompt to complete morning saliva sample.

Question: “Was a saliva sample taken?”

Response Option Format: Radio Buttons

Response Options: Yes, No

Pages 2 and 3

Purpose: Locations of pain. Page 2 was an anterior view of a body map (also known as a body diagram, body outline, pain chart, manikin), and page 3 was a posterior view. The body map was a representation of a young male wearing white shorts. A male form was chosen to discretely allow for minimal clothing. The anterior screen included an umbilicus and both the anterior and posterior screens identified the left shoulder with an arrow for orientation. Body maps were used to calculate the total number of body locations in pain at each time point, which was a sum of the number of locations highlighted.

Reliability and Validity: No studies were found that compared the reliability and validity of different tools for identification of body locations in pain by youth. Savedra et al. compared use of the body outline of the Adolescent Pediatric Pain Tool (APPT) to identification of location of pain by pointing among 175 hospitalized youth aged 8 to 17 years.⁽²⁸⁵⁾ A high degree of agreement was found between these two methods of measurement ($\kappa = 0.8$ to 0.9). No studies were found that examined the reliability of body maps for pain in children. However, Weiner et al. found good to excellent agreement ($\kappa = 0.6$ to 0.9) on test-retest scores of the APPT body map for assessment of pain location in 60 elderly residents in nursing homes (mean age = 80).⁽²⁸⁶⁾ No research was found that investigated the youngest age at which a body map could be used independently; however, von Baeyer et al. recommend that unassisted use of body maps be limited to youth aged 8 years and older.⁽²⁸⁷⁾

Differences with e-Ouch: The body location map differed from that of the e-Ouch diary. On the e-Ouch diary, participants could highlight up to 20 large joints; therefore, headache, abdominal pain, chest pain, or pain on body locations other than the joints (e.g. mid-thigh) could not be highlighted. In the PInGo the whole body was demarcated to allow participants to identify non-joint related pains. Participants in this study included youth with non-JIA persistent pain, who

would be expected to identify extra-articular locations of pain. Demarcations were made along anatomically relevant sections of the body. For example, the right lower extremity was divided into three sections: right anterior and lateral hip to the mid-thigh, mid-thigh to the mid-calf and below mid-calf, inclusive of the ankle and foot. Demarcations were made as small as possible without compromising precision. Given the limited real estate of the iPod screen and the sensitivity of the touch screen technology, a greater number of demarcations would have made precision more difficult and time consuming without necessarily improving the validity or relevance of the information provided. Demarcations were also made in such a way that pain reports could be computed into a score for wide-spread pain for future analyses. The American College of Rheumatology (ACR) defines widespread pain as pain in the upper and lower half of the body (transverse plane through the umbilicus), the right and left hemispheres (sagittal plane midline) and along the axial skeleton. ⁽²⁸⁸⁾

Question: "Touch the parts of the body to show where you have PAIN or HURT right now. Shake to clear."

Response Option Format: Sixteen anterior and 17 posterior body locations could be highlighted by touching the screen on the part of the body that was in pain. To erase a location that was highlighted, participants could double touch the location or shake the iPod to clear all highlighted locations.

Response Options: See Appendix M

Page 4

Purpose: Pain intensity VAS

Reliability and Validity: The VAS is a commonly used measurement tool for self-reported continuous measures which is most often presented as a 10 cm long, horizontally oriented line in a paper-based format. Respondents make a vertical mark along the line to indicate a score which is measured from the left anchor. In a horizontally oriented VAS, verbal anchors with minimal values are at the far left and maximal values at the far right. VAS scales vary in the wording of anchors and the length of the line. The VAS showed good to excellent test-retest reliability when used by healthy children to score weights of unmarked containers on two sessions separated by two weeks. ⁽²⁸⁹⁾ Median between session correlation coefficients of $r=0.70$ were found with 5 to

6 year olds and $r=0.99$ for 13 to 15 year old adolescents. Stinson et al. found moderate positive correlations ($r=0.55$) between the average weekly VAS scores for pain intensity collected on an electronic diary (e-Ouch) and recalled average weekly pain scores. ⁽¹⁹⁾ Stinson et al. also found that VAS pain intensity scores collected on electronic diary were sensitive to change in pain following joint injection (Week 1 to Week 3 $F[1,70] = 23.59, p<0.01$), thereby establishing convergent and construct validity in the use of the VAS in an electronic diary pain assessment. ⁽¹⁹⁾ Sensitivity, validity and reliability of the VAS for pain intensity ratings by children have been extensively studied. ^(58, 290-296) Seymour et al. found strong correlations ($r=0.86$ to 0.95) between VAS of differing line lengths for measuring dental pain in adults. ⁽²⁹⁷⁾ Sindhu et al. found high test-retest reliability of a 5 cm electronic version of the VAS for measuring pain in adults with upper extremity injuries. ⁽²⁶³⁾

Differences with e-Ouch: The wording of the upper anchor for the VAS differed between the PInGo and e-Ouch. There are currently no universally accepted standards for wording of anchors in VAS scales. ^(108, 298) The upper anchor is meant to represent a maximum amount of pain for the responder. The e-Ouch diary used the wording "Very much pain," which was changed to "Most pain possible;" another commonly used wording for the upper anchor.

Question: "Drag the mark to show how much PAIN or HURT you have right now."

Response Option Format: Five centimetre VAS with a sliding marker that oriented to the mid-line when the screen was opened (this was consistent for all PInGo VAS scales).

Response Options: The anchors for the VAS were "No pain" at the far left at 0 cm and "Most pain possible" at the far right at 5 cm. Output was hidden from the respondent but was transmitted as a score between 0 and 100 at increments of 1 (this was also consistent for all VAS scales on the PInGo).

Page 5

Purpose: Pain affect/unpleasantness.

Differences with e-Ouch: None

Question:"Drag the mark to show how UNPLEASANT your pain is right now."

Response Option Format: Sliding 5 cm VAS.

Response Options: Anchors were "Not at all unpleasant" at the far left and "Very unpleasant" at the far right.

Page 6

Purpose: General interference of pain with life.

Differences with e-Ouch: None

Question: "Drag the mark to show how much your pain is getting in the way of THINGS YOU DO right now."

Response Option Format: Sliding 5 cm VAS.

Response Options: Anchors were "Doesn't get in the way at all." at the far left and "Totally gets in the way" at the far right.

Page 7

Purpose: Interference of pain with walking.

Differences with e-Ouch: None

Question: "Drag the mark to show how much your pain is getting in the way of WALKING right now."

Response Option Format: Sliding 5 cm VAS.

Response Options: Anchors were "Doesn't get in the way at all." at the far left and "Totally gets in the way" at the far right.

Page 8

Purpose: Interference of pain with sleeping

Differences with e-Ouch: None

Question: "Drag the mark to show how much your pain got in the way of SLEEPING last night."

Response Option Format: Sliding 5 cm VAS.

Response Options: Anchors were "Didn't get in the way at all" at the far left and "Totally got in the way" at the far right.

Page 9

Purpose: Interference of pain with enjoying life.

Differences with e-Ouch: None

Question: "Drag the mark to show how much your pain is getting in the way of ENJOYING LIFE right now."

Response Option Format: Sliding 5 cm VAS.

Response Options: Anchors were "Doesn't get in the way at all." at the far left and "Totally gets in the way" at the far right.

Page 10

Purpose: List of words to describe the pain experience.

Differences with e-Ouch: The e-Ouch included 30 word descriptors that included sensory, affective and evaluative words, but no temporal descriptors. It is a limitation of the current research that due to the restricted real-estate (screen space) of the iPod touch screen, a list of only 12 words or phrases could be provided on a single screen, thereby limiting the number of descriptive words that could be provided on the checklist. Only one screen of descriptive words was included in the diary to avoid the need for children to move forward and backward between two or more pages to compare and select words. Six words were selected from the APPT list of sensory descriptive words. The APPT contains 56 descriptive words that are divided into similar groupings of sensory (37 words), affective (11 words) or cognitive-evaluative (8 words) qualities of pain. One word from each sensory grouping was selected to represent that subsection. These were selected because they are words or phrases frequently chosen by youth with a variety of persistent or acute pain conditions. ^(58, 101, 299-301) A further five words were selected from a list of temporal descriptive words based on the work of Savedra et al. on how youth describe the temporal dimension of pain. ⁽¹¹¹⁾ These words or phrases were selected because they were those most frequently used by children to describe onset (comes all of a sudden), duration (once in a while, never goes away) and change in pain over time (steady, comes and goes). A relatively large proportion of temporal words were included since the basis of this research is on the temporal variability of pain. A final response option was available for participants to select if none of the available words were chosen. Participants were instructed to try to describe their pain

in their own words in the open texting field on the final screen if they selected the neutral response.

Question: "Touch the words that best describe how your pain feels right now."

Response Option Format: Check list buttons with single radio button neutral option

Response Options:

Sensory words: Aching, throbbing, sharp, burning, pinching, stinging

Temporal descriptors: Steady, once in a while, never goes away, comes and goes, comes all of a sudden.

Neutral: None of these describe my pain

Page 11

Purpose: Stiffness question

Differences with e-Ouch: None

Question: "Drag the mark to show how STIFF you are right now."

Response Option Format: Sliding 5 cm VAS.

Response Options: Anchors were "Not at all stiff" at the far left and "Very stiff" at the far right.

Page 12

Purpose: Emotional valence facial scale. The emotional valence question was one of two questions used to measure mood/emotional affect using the two dimensional circumplex model of affect of Russell. ⁽⁴⁸⁾

Reliability and Validity: The original FAS has demonstrated acceptable reliability and validity for quantification of magnitude of spatial dimensions and aversive nature of hypothetical pain scenarios. ⁽³⁰²⁾ A limitation of the current study was that the psychometric properties of the modified FAS were not examined. The modified FAS had 7 response options as opposed to 9 in the original FAS. The graphic design of the faces was modified to match the face of the body diagram. The response outcome was further simplified on analysis into a dichotomous variable of negative/neutral valence or positive valence. Testing of the psychometric properties of the modified FAS was not within the scope of the study and would be a valuable future study;

however, since mood was used in analysis, the study findings should be interpreted in light of this limitation.

Differences with e-Ouch: The e-Ouch diary included a question about pain interference with mood, but did not directly measure mood or emotional affect. A modified version of the Facial Affective Scale was used as a measure of emotional valence. The original Facial Affective Scale (FAS), ^(289, 302) used to assess the aversive component of pain, has nine faces arranged in a semi-circular order with a neutral face at the apex of the semi-circle on the left and four faces showing increasing grades of positive affect along the upper arm of the semi-circle and four faces showing increasing grades of negative affect along the lower arm of the semi-circle. Since the FAS was used in the circumplex model of affect to compute a categorical mood score, the modified FAS only needed to distinguish positive valence from negative or neutral valence. Therefore, for the purposes of this study, the FAS was modified by removing of one of the positive and one of the negative faces from the arms of the semicircle. This modification allowed the size of the faces of the scale to be a reasonable size on the iPod screen. The modifications made the scale similar to the Children's Feeling Scale developed by Hulley et al., ⁽²⁴⁶⁾ with the primary difference being the arrangement of the seven faces in a semi-circle, in the same fashion as the Facial Affective Scale, rather than in a straight line. Graphics of the face were modified to match the faces to the face of the body map.

Question: "Touch the face that best shows how GOOD or BAD your mood is right now."

Response Option Format: Facial scale

Response Options: 7 response categories; 3 positive, 1 neutral and 3 negative with anchors "very good" at the end of the upper arm and "very bad" at the end of the lower arm (Appendix N)

Page 13

Purpose: Activation. The activation question was the second of two questions used to measure mood/emotional affect using the two dimensional circumplex model of affect of Russell. ⁽⁴⁸⁾

Reliability and Validity: The original Felt Arousal Scale showed moderate to high correlations (0.45 to 0.70) with Lang's Arousal scale. ⁽²⁴⁶⁾ The modified version of the scale developed by Hulley et al. for children was developed through iterative pilot testing with a group of 20 healthy youth between 5 and 10 years of age in which children were required to match the faces of the

scale with the correct verbal and numeric values. ⁽²⁴⁶⁾ The adapted version of the scale showed responsiveness in appropriate changes pre and post walking activity and sensitivity to the dose of activity.

Differences with e-Ouch: The e-Ouch diary included a question that was very similar in format and wording, but was used as a measure of fatigue. This question used the Felt Arousal Scale of Svebak and Murgatroyd ⁽²⁴⁸⁾; however, the original anchors of this scale were “low arousal” on the left anchor and “high arousal” on the right anchor. A study by Hulley et al. modified the anchors of the scale to “very sleepy” and “very awake” for use with children.

Question: "Drag the mark to show how AWAKE or SLEEPY you feel right now."

Response Option Format: Sliding 5 cm VAS.

Response Options: Anchors were "Very SLEEPY" at the far left and "Very AWAKE" at the far right.

Page 14

Purpose: Part 1 - Pharmacologic treatments for pain since the preceding diary entry.

Part 2 – Effectiveness of the treatment in relieving pain symptoms.

Differences with e-Ouch: The evening survey of the e-Ouch diary included a two part question about medication use for pain. The question was, "Please tell us about the pain medicines you have taken today." Participants were provided a checklist of common pain medications which included an option for "other" if the medication was not on the list. If the "other" option was selected, an open texting field would appear for participants to note the name of the medication. For each medication selected, a drop-down menu would appear with Likert scale asking participants to rate how effective the treatment was in relieving their pain.

Question: There were two parts to the question. In the first part, participants were asked, “Did you use any medicine for your pain in the last 2 hours?” If participants answered positively to the first part, a second question would appear which read, “Touch the mark and move it to show how much the treatments helped give you relief from your pain. Please record the name on the Treatment Log.”

Response Option Format: Part 1 – radio buttons

Part 2 – 5 cm sliding VAS

Response Options: Part 1 – “yes” or “no.”

Part 2 – Anchors were "No relief at all" at the far left and "Complete relief" at the far right.

Page 15

Purpose: Non-pharmacologic treatments for pain since the preceding diary entry.

Differences with e-Ouch: The evening survey of the e-Ouch diary included a two part question about non-pharmacologic treatments used for pain that had a similar format to the pharmacologic question described above. The question asked "Please tell us about the other things you used to REDUCE your pain today." A checklist of options was provided with contingency based questions for each treatment asking participants to rate effectiveness of the intervention.

Question: Similar to page 14, there were two parts to this question also. In the first part, participants were asked, "Did you use any other type of treatment to ease your pain in the last 2 hours?" If participants answered positively to the first part, a second question would appear asking, "Drag the mark to show how much the treatments helped give you relief from your pain. Please record the treatment on the Treatment Log."

Response Option Format: Part 1 – radio buttons

Part 2 – 5 cm sliding VAS

Response Options: Part 1 – "yes" or "no."

Part 2 – Anchors were "No relief at all" at the far left and "Complete relief" at the far right.

Page 16

Purpose: Open texting field.

Differences with e-Ouch: The e-Ouch diary also included an open texting field.

Question: "Please enter any notes for this survey entry."

Response Option Format: A standard format QWERTY key board would appear when participants touched the empty box on the screen.

Response Options: No limitations. At the enrolment visit, participants were instructed to text anything they wanted to about the study or their pain. They were instructed to use the texting option to enter descriptions of pain, the name of medications taken for pain or non-

pharmacologic measures for pain management used since the preceding diary entry. They were also given a paper log to record pharmacologic and non-pharmacologic treatments (Appendix O).

4.2.5.1.1 Pilot testing of PInGo functionality and study protocol

Three healthy children were recruited to pilot test the enrolment visit and iPod app prior to data collection with the clinical population. The purpose of the pilot test was to assess the device for problems with data transmission between the iPod and the server, to test the ease of use of the iPod app for youth in a school setting, test the alarm, practice the enrolment training, consent and anthropometric data collection. The three children were a convenience sample of family members and friends of the investigator, aged 10, 13 and 14. For the pilot test, the youth went through the entire consent and enrolment procedure process but only followed the electronic diary protocol for the four days. They were not required to wear the accelerometers, provide saliva samples, or fill in the questionnaires. The youth were then asked to reiterate the study protocol in their own words to determine whether or not they understood the study protocol and enrolment procedure. No difficulties were detected in their ability to understand the vignette and study procedures required for the study. Youth were asked to fill in the survey as if they had pain and go through the entire app on all but one diary entry even if they did not have pain at the time. They were asked to report no pain on one entry. No difficulties with data transmission were detected during the pilot test. The youth were asked if they had any difficulty with using the iPods at school. No issues were reported. On pilot testing, the investigator noticed one error in the PInGo app in that forward progress was possible on some pages even if the participants did not provide an answer. This was corrected by the programmers prior to enrolment of the clinical population.

4.2.5.2 Questionnaires

4.2.5.2.1 Demographic questionnaire

The demographic questionnaire (Appendix P) was designed for the current study and was completed by parents/guardians. It included a check list of ethnicity from the Statistics Canada standards for classification.⁽³⁰³⁾ Data on ethnicity were collected for two reasons. First, the

characteristics of the participants were examined to determine generalizability of results, and second, ethnicity was collected for inclusion as a predictor variable in the logistic regression and GEE analysis. The demographic questionnaire included four questions for computation of the Hollingshead four factor index of socioeconomic status (SES).⁽³⁰⁴⁾ Scores for the Hollingshead measure of SES range from 8 to 66 which are based on weighted scores for education and occupational codes for the parents, and are trichotomized into low SES for scores from 8 to 27, medium SES for scores from 28 to 47, and high SES for scores from 48 to 66.⁽³⁰⁵⁾ SES was included as a predictor variable in the logistic regression and GEE analysis. The Hollingshead is one of the most frequently used measure of SES.^(306, 307) The Hollingshead measure of SES has a moderate to strong correlation with family income ($r=0.78$).⁽³⁰⁴⁾ Inter-rater reliability is moderate to strong, ($r=0.73$ to 0.95 ; % agreement 67 to 96) and inter-measure concordance with two other measures of SES was moderate to strong ($r=0.42$ to 0.92 ; $kappa = 0.37$ to 0.67).⁽³⁰⁶⁾

4.2.5.2.2 Childhood Health Assessment Questionnaire (CHAQ)

The Childhood Health Assessment Questionnaire (CHAQ) is a 36 item composite index of physical function and independence with activities of daily living that was developed for youth with arthritis between the ages of 1 to 19 years (see Appendix Q). The CHAQ has eight domains of physical function that are scored on four point ordinal scales. Scores are computed into a measure that ranges from zero (no disability) to three (highest level of disability). The CHAQ takes approximately 10 minutes to complete. Both self-report and proxy report versions are available. For this study parents/guardians completed the CHAQ to minimize the responder burden on the participants. Good agreement has been found between self-report and proxy report measures of the CHAQ.⁽³⁰⁸⁾ The CHAQ shows high positive correlation with measures of JIA disease severity, negative correlation with proximal muscle strength, high test-retest reliability and responsiveness to treatment.^(309, 310)

4.2.5.2.3 Physical Activity Questionnaire for Older Children or for Adolescents

The Physical Activity Questionnaire for Older Children (PAQ-C) or for Adolescents (PAQ-A) is a general physical activity questionnaire that was completed by the participant. The PAQ-C for older children and the PAQ-A for adolescents are both 7-day recall self-report measures of physical activity developed for children aged 8-12 years (PAQ-C) and aged 13-18

years (PAQ-A).⁽³¹¹⁻³¹³⁾ The PAQ questionnaires demonstrated acceptable validity with a moderate correlation with objective activity monitoring with accelerometer ($r=0.56$ to 0.63) and good internal consistency (Cronbach's $\alpha = 0.72$ to 0.88).⁽³¹²⁾ The PAQ-C consists of 11 questions on the frequency, mode and intensity of activity participation over the recall period. The PAQ-A has one less question; the question about activity during recess has been removed. The PAQ is a composite score that produces a continuous outcome ranging from one (lowest activity level) to five (highest activity level). The PAQ takes approximately five minutes to complete (see Appendices R and S) and was selected as the top choice of physical activity surveillance questionnaires in a recent systematic review based on comprehensiveness, psychometric properties, and feasibility of use.⁽³¹⁴⁾

4.2.5.2.4 Pediatric Quality of Life Questionnaire

The Pediatric Quality of Life Questionnaire (PedsQL 4.0) Generic Core Scale is a licensed 23 item questionnaire with four dimensions which is used to assess health related quality of life in children with rheumatic disease between the ages of 2 and 18 years.⁽³¹⁵⁾ Items on the PedsQL are rated on a 5-point Likert scale. Scores from the PedsQL are transformed into a continuous scale ranging from 0 (lowest quality of life) to 100 (highest quality of life). Permission was gained to use the measure. The PedsQL was completed by the participant. The PedsQL has demonstrated good reliability with internal consistency (Cronbach's $\alpha = 0.88$ to 0.90).⁽³¹⁵⁾ The PedsQL is able to distinguish between healthy children and those with rheumatic disease,⁽³¹⁵⁾ and has demonstrated sensitivity to change in disease status over time in youth with arthritis, and children undergoing treatment for fractures.⁽³¹⁶⁾ The PedsQL data was not included in analysis to narrow the scope of the study, but was collected for future analyses.

4.2.5.3 Accelerometry

Physical activity was objectively measured by Actical accelerometer (Mini Mitter Co., Inc., Bend, OR). The Actical is a wrist watch sized light weight omnidirectional accelerometer which is able to sense accelerations (movement) in all directions, and is a direct measure of physical activity. The Actical is considered a valid and reliable measure of physical activity for healthy children and adolescents.⁽³¹⁷⁾ Trost et al. reported moderate to strong correlations ($r=0.53$ to 0.92) between accelerometer counts and measures of energy expenditure derived from

indirect calorimetry measurement (VO_2).⁽²⁴²⁾ Actical accelerometers demonstrated higher intra- and inter-instrument reliability compared to two other commercial models.⁽³¹⁸⁾ Accelerometers were purchased for the study and borrowed from the accelerometer pool in the Department of Kinesiology at the U of S. Accelerometers used in the study were calibrated by a research associate in the Department of Kinesiology, U of S, prior to first use.

The accelerometers were programmed to sum accelerations over 15 second epochs, which is recommended for field based activity research in children.⁽²⁴²⁾ Each device was individually calibrated to the participant's age, sex, weight and height prior to wear. Raw data from the accelerometers were entered into a custom designed software program⁽²⁴³⁾ for reduction to minutes of sedentary, light, or moderate to vigorous physical activity (MVPA) based on age adjusted regression equations for metabolic equivalent calculations of energy expenditure.⁽²³⁹⁾

Accelerometer data was analyzed by windows of wear that coincided with the PInGo diary entries. The PInGo diary entries were scheduled for 8:00 am, 10:00 am, 12:00 noon, 2:00 pm, 4:00 pm, 6:00 pm and 8:00 pm. Activity windows were cut from the two hours immediately preceding the scheduled PInGo entry from 6:00 to 7:59 am, 8:00 to 9:59 am, 10:00 to 11:59 am and so on. PInGo diary entries were also time stamped. Diary entries were examined to determine how close to the scheduled time the entries were made.

4.2.5.4 Salivary cortisol

Cortisol levels were determined from the saliva samples by enzyme linked immunosorbent assay (Neogen, Lexington, KY). All saliva samples were analyzed by the same laboratory technician at the Pediatric Rheumatic Disease Research Laboratory at the U of S. Saliva samples were thawed and analyzed in batches. Cotton swabs were centrifuged and each saliva specimen was analyzed in duplicate with seven calibrator and one control sample on each microtiter plate, according to the manufacturer's analysis protocol.

Each individual provided up to eight saliva samples. Diurnal variability of cortisol was determined by linear regression of each individual's cortisol concentration by time of day which provided an intercept and slope for each individual.⁽³³⁾ The linear regression parameter estimates were converted into a nominal categorical variable according to the criteria described by Smyth

et al. to describe the slope as either normal (down-going from morning to evening; $\beta \leq -0.05$) or flat (no decline during the day; $\beta > -0.05$).⁽³³⁾

4.2.5.5 Anthropometric data

Weight was measured twice on a digital scale in kilograms (kg) and recorded to the nearest 0.1 kg. Participants were asked to stand in the centre of the scale without support, weight evenly distributed between both feet, with arms at their sides. Weight was taken with participants in minimal clothing (pants or shorts and light shirt) and without footwear. If there was a difference in the two measures, the average weight was recorded.

Standing and sitting heights were measured with a wall mounted stadiometer following the stretch stature method.⁽²⁸⁰⁾ Standing height was recorded with the participant standing without footwear, with feet together and flat on the floor, with the back and buttocks against the stadiometer. The investigator held the participant's head in the Frankfort plane and transmitted an upward pressure through the mastoid processes while the participant took a deep breath. An assistant held the head board of the stadiometer firmly on the vertex of the head. Height was measured to the nearest 0.1 cm. This measurement was repeated twice and an average of the two measures was taken. If there was greater than 0.4 cm difference in the two scores, a third measurement was taken and the median value was recorded.

Sitting height was measured with participants sitting on a firm plastic stool with the back and buttocks against the stadiometer and hands on the lap. The same stretch stature method was used for sitting height. Two repeated measures were taken and averaged, or if greater than 0.4 cm difference between the first two measures, a third was taken and the median score recorded. Sitting height was calculated as the measured height minus the height of the box. To ensure that the plastic stool was not flexing with the participant's weight, two research associates were asked to stand on the stool while the height of the stool was measured with the stadiometer. The weight of the heavier research associate was approximately 78 kg. The plastic stool height did not change with the weight of either of the associates; therefore, the stool was considered a stable surface for these measurements.

4.2.6 Analytic Procedures

4.2.6.1 Case selection and imputations

Measures of dispersion were computed for the entire dataset and for each individual. Data were examined for missingness. Cases were eliminated from analysis if no pain was reported over the 28 time points or if fewer than 20 of the 28 data points were reported ($20/28 > 70\%$ completion rate). Based on the results of Study 1, individual TOD means were calculated and used as imputations for missing data points for the cosinor analysis.

4.2.6.2 Cosinor analysis and logistic regression

Cosinor analyses were conducted on individual time series (Objective 2.1). Parameter estimates from the cosinor analyses were retained for the logistic regression in the second stage of the two-stage analysis (Objective 2.2). In the same method used for Study 1, 1000 simulated matrices (30x28) were computed using Monte Carlo bootstrapping methods and analyzed by cosinor analysis. The range of proportions of significant cosinor analyses were compared to that found in the clinical dataset to determine if the proportion of significant cosinor analyses found in the original dataset exceeded that found by chance in the simulated dataset. Similar to the method described for Study 1, univariate analysis was conducted on disease and demographic variables with a screening criterion of $p < 0.25$ for inclusion in the full model. The final model included variables that were significant predictors ($p < 0.05$) of the probability of having a significant cosinor analysis. Cosinor outcomes and the results of logistic regression were compared between Study 1 and Study 2. Variables that were found to be significant in the logistic regression of Study 1 were considered biologically relevant for inclusion in the full model of Study 2 logistic regression and GEE analysis of Study 2 as main effects and in interactions.

4.2.6.3 Generalized estimating equations

GEEs were computed in a similar manner to Study 1. GEEs were conducted to examine the data for time of day effect, and to examine the relationship between physical activity and pain, controlling for the within-day variability of mood (Objective 2.3). GEEs were conducted on raw data without imputations with pain as an ordinal categorical variable.

4.2.7 Ethical considerations

Every measure was taken to maintain confidentiality of the data and protect the rights of participants. All procedures were approved by the Institutional Behavioural Research Ethics Board of the University of Saskatchewan and operational approval was obtained from the Saskatoon Health Region. Informed consent was obtained from parents/guardians and assent from participants. The assent form was read aloud to participants under the age of 11. Confidentiality of data was maintained by use of participant identification codes, initial contact by letter or by a research associate not involved in the care of the participant. At enrolment participants were informed that they could refuse to participate or withdraw at any time without influencing subsequent health care. All data collected were stored in locked filing cabinets or a pass-word protected computer in a locked office. Compensation for involvement in the research was only mentioned after participants agreed to enrol in order to avoid potential coercion. Enrolment and training took place at a time and place that was convenient for the participant, such as in conjunction with a regularly scheduled clinical visit or at the participant's home. Names, addresses and contact information were kept by the investigator in a locked office for the purposes of collecting equipment and mailing gift cards. These were kept on a single contact list that was shredded once the gift cards were sent. All reporting of data was done in aggregate form or using participant identification codes.

CHAPTER 5

5 RESULTS

5.1 Study 1: Within-day variability of pain in youth with JIA

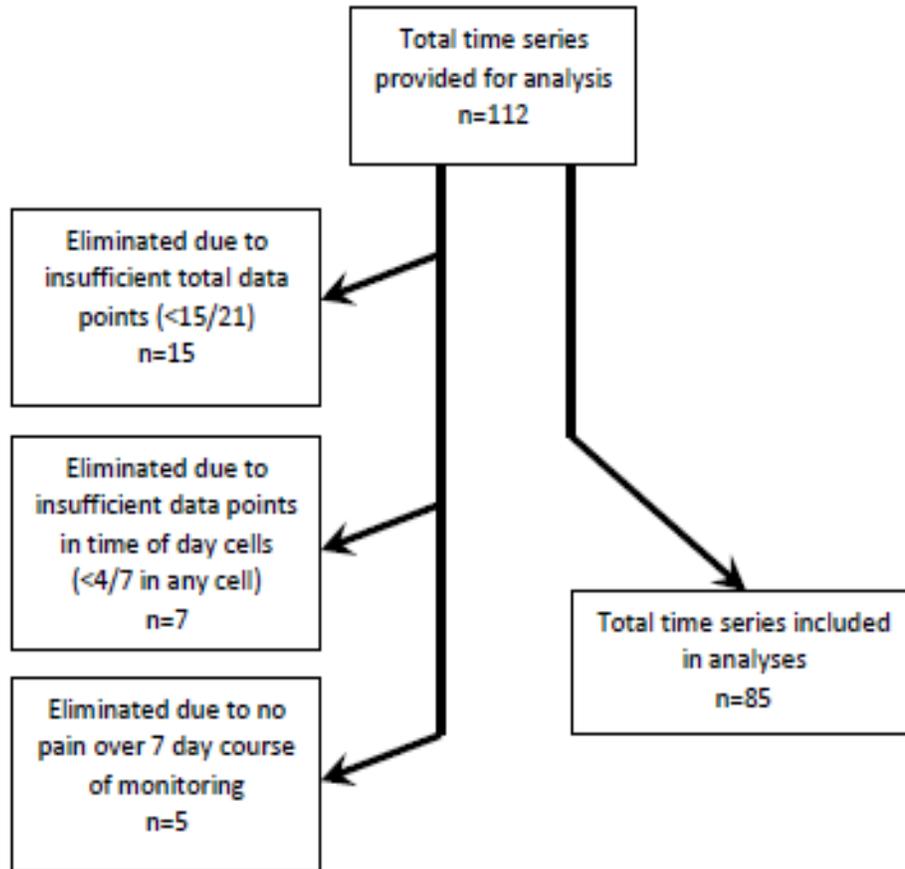
5.1.1 Data Management

Electronic diary, questionnaire and clinical data from 112 participants recruited for the Stinson et al. study between January, 2005 and January, 2006 in Toronto, Ontario, Canada were transmitted for analysis in Study 1. Data were analyzed for the current research in PASW Statistics 17, Release Version 17.0 (SPSS Inc., 2009, Chicago, IL, www.spss.com). As explained in Chapter 4, 76 youth provided data up to three times per day for two weeks and 36 youth provided data up to three times daily for three weeks. Only data collected during the first week were used; therefore, each participant contributed pain intensity data up to three times daily for seven days, for a total potential data set of 112 time series, each having 21 data points.

5.1.2 Case Selection

Data were first examined for missingness and cases were included for analysis based on two criteria for completeness. Time-series were required to have an overall completeness of 70% (at least 15 of 21 time points), and morning, afternoon and evening cell frequencies of 60% (at least 4 of 7 time points). Since cosinor analysis cannot be conducted on a series of no-pain, cases were eliminated if the participant reported no pain (pain score equal to zero) over the 21 time-points. A flow diagram depicting case selection based on data completeness is presented in Figure 5-1. A total of 85 time series were included in the final analysis yielding a selection rate of 76% ($n=85/112$) of eligible time series from the original data set.

Figure 5-1: Flow Diagram of Case Selection



5.1.3 Demographic and Disease Characteristics of the Sample

Demographic and disease characteristics of the participants included in analysis and cases excluded from analysis for Study 1 are presented in Table 5-1. Mean age of participants was 13.1 years (SD = 2.4; range = 8 - 17 years) and 72.9% of the participants were female. Rheumatoid factor negative (RF-) polyarticular JIA was the most common disease subtype (37.6%). The mean disease duration was 4.8 years (SD = 4.4; range 0.1 - 14.8 years), and the mean disease severity rated by pediatric rheumatologists on a 100 mm VAS ranging from 0 (least severe) to 100 (most severe) was 30.7(SD = 24.0; range 0.5 - 89.0). Participants had a wide range of joint involvement from 1 to 58 active joints assessed at a clinical visit by a rheumatologist. T-tests and non-parametric chi-squared tests were conducted to compare cases included in analysis and those excluded in age, diagnosis, disease duration, disease severity or total number of active joints.

There were no significant group differences in these variables. There were insufficient cases in the no-pain group to conduct a separate analysis; therefore, these cases were included with those eliminated for missingness to determine if the total group differed significantly from those included in the analysis.

Table 5-1: Study 1 demographic and disease characteristics

Characteristic	Participants included in analysis n = 85			Excluded cases Missing data n=27 No pain n=5		
	n (%)	M (SD)	Range	n (%)	M (SD)	Range
Age (years)		13.1 (2.4)	8 to 17		13.0 (2.8)	9 to 17
Male	23 (27.1)			6 (22.2)		
Female	62 (72.9)			21 (77.8)		
Diagnosis						
Systemic Onset	12 (14.1)			2 (7.4)		
Oligoarticular	19 (22.4)			6 (22.2)		
Poly RF -	32 (37.6)			9 (33.3)		
Poly RF +	4 (4.7)			2 (7.4)		
Psoriatic	6 (7.1)			4 (14.8)		
Enthesitis	8 (9.4)			4 (14.8)		
Other	4 (4.7)			0 (0)		
Disease Duration (years)		4.8 (4.4)	0.1 to 14.8		4.8 (3.9)	0.2 to 16.0
Disease Severity (100mm VAS) PGADS		30.7 (24.0)	0.5 to 89.0		29.6 (28.2)	1.0 to 90.0
Total Number of Active Joints		6.74 (8.9)	1 to 58		9.0 (11.6)	1 to 42

Poly = polyarticular

5.1.4 Pain Intensity Characteristics of the Sample

Characteristics of the pain intensity reports collected in the first week with the e-Ouch diary for those participants included in the analysis (n=85) are presented in Table 5-2. Mean pain for the sample was of mild intensity at 23.9 on a 0 to 100 scale (SD = 27.9; range 0 - 100). Mean

pain intensities computed for each participant ranged from 0.63 to 77.4 and the majority of individual pain distributions were positively skewed (range of skewness -1.4 to +4.6). Median pain intensity was 14 (IQR = 36.0) with a positively skewed distribution (skew = 1.13; kurtosis = 0.16).

Table 5-2: Study 1 characteristics of pain intensity reports (n=85)

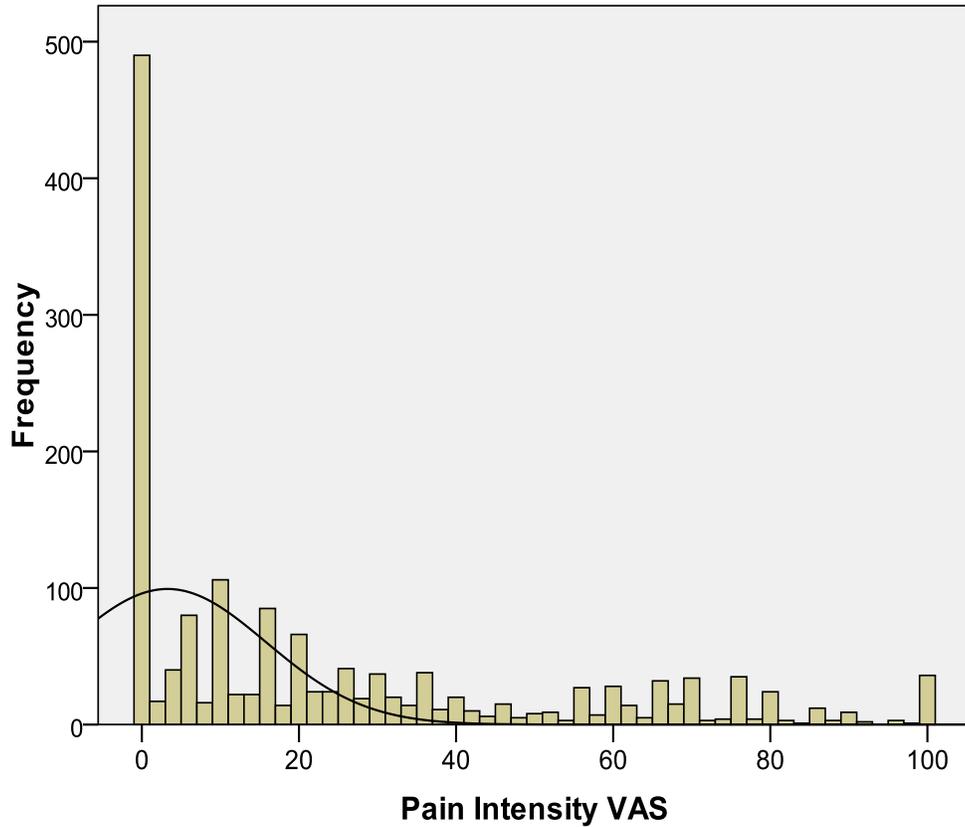
Characteristic	Total Sample Pain Intensity	Individual Range
Number (%)	1564 (87.6)	15 to 21
Mean (SD)	23.9 (27.9)	0.63 to 77.4
Median (IQR)	14.0 (36.0)	0 to 85
Range	0 - 100	
Skewness (SE)	1.13 (0.06)	-1.4 to +4.6
Kurtosis (SE)	0.16 (0.12)	

% = percentage
SD = standard deviation

IQR = interquartile range
SE = standard error

Figure 5-2 depicts the distribution of the total sample. The large proportion of zero scores (27.5 %) give the pain intensity data a bimodal distribution with both discrete properties (pain/no pain) and continuous properties when pain is reported as present (1 - 100). This is considered a Tweedie class of distribution.⁽³¹⁹⁾ Given that these data are not normally distributed and resistant to transformation, the pain intensity data was converted to an ordinal categorical variable for the GEEs.

Figure 5-2: Frequency distribution of pain intensity reports



5.1.5 Imputations

Measures of dispersion for pain intensity data were compared between the original non-imputed dataset, the dataset with TOD imputations and the dataset with random imputations; see Table 5-3. Mean pain differed slightly but non-significantly between the two methods of imputation ($p=0.16$, unpaired student's t-test). The TOD imputed dataset was more similar to the original non-imputed dataset on measures of dispersion than those calculated with the random imputation method. Therefore, TOD means were selected as a better representation of the original dataset and the method of imputation. In addition, this method was thought to preserve any potential structure (systematic variability) within the data. However, if structure did not exist within the data, use of TOD means would result in pain scores that deviated towards the mean, hence reducing the likelihood of obtaining a statistically significant zero-amplitude test on cosinor analysis and production of more conservative estimates.

Table 5-3: Comparison of imputation methods

Characteristic	No Imputation	TOD Imputation	Random Imputation
	n=1564	n=1785	n=1785
Mean (SD)	23.9 (27.9)	24.0 (27.0)	25.3(27.8)
Median (IQR)	14 (36)	15 (37)	15(40)
Skewness (SE)	1.13 (0.06)	1.11 (0.06)	1.03 (0.06)
Kurtosis (SE)	0.16 (0.12)	0.19 (0.12)	-0.05 (0.12)

TOD = time of day

IQR = interquartile range

SD = standard deviation

SE = standard error

5.1.6 Cosinor Analysis

Cosinor analysis (Objective 1.1) produced significant fit ($p < 0.05$) for 19 of the 85 time series (22.4%). A further 6 time series (7.1%) were borderline significant ($p < 0.10$). Table 5-4 presents the distribution of the parameter estimates obtained from cosinor analysis. Acrophase values were converted to a categorical variable to be more meaningful. Acrophase occurred in the morning for 11 (11/19 = 57.9%) time series, in the afternoon for 1 (1/19 = 5.3%) time series and in the evening for 7 (7/19 = 36.8%) time series that had a significant zero amplitude test (n=19 youth). Figures 5-3a to 5-3i are a selection of chronograms of the time series showing both statistically significant ($p < 0.05$) and non-significant zero amplitude tests overlaid with the fitted cosinor curve. These were selected as a representation of the range of variability observed in terms of significance on the zero amplitude test and high or low within-day variability. Figures 5-3a, 5-3b and 5-3c are time series with significant zero amplitude tests with high within-day variability (amplitude > 10). Figure 5-3d is a significant time series with low within-day variability. Figures 5-3e, 5-3f and 5-3g are non-significant with high within-day variability and Figures 5-3h and 5-3i are non-significant with low within-day variability.

Table 5-4: Characteristics of cosinor analysis parameter estimates

Parameter	Significant zero amplitude test ($p < 0.05$) n=19		Borderline zero amplitude test ($0.05 < p < 0.10$) n=6		Non-significant zero amplitude test ($p > 0.10$) n=60	
	Mean (SE)	Range	Mean (SE)	Range	Mean (SE)	Range
Mesor (0-100)	33.9 (6.1)	0.1 to 85.8	19.4 (5.8)	4.4 to 45.5	21.6 (2.3)	0.3 to 77.1
Amplitude (0-100)	21.4 (4.1)	1.7 to 19.2	11.1 (2.2)	5.5 to 19.2	7.6 (0.9)	0.6 to 24.9

SE = Standard Error

Figure 5-3: Study 1 Time Plots with Fitted Cosine Curves

Figure 5-3a: A01 significant zero amplitude ($p=0.04$), mesor=44.6, amplitude=18.9, evening acrophase

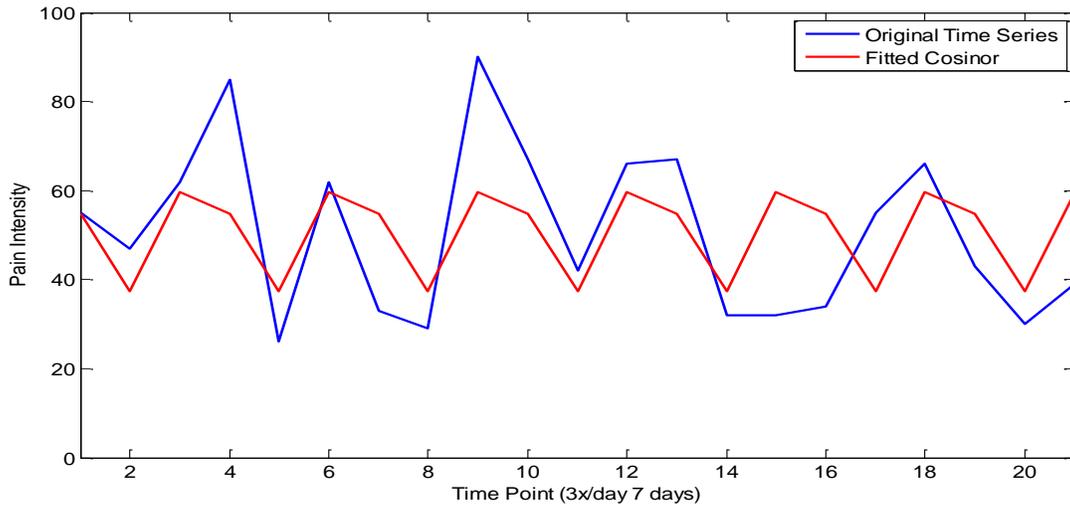


Figure 5-3b: A14 significant zero amplitude ($p<0.01$), mesor=48.5, amplitude=29.8, morning acrophase

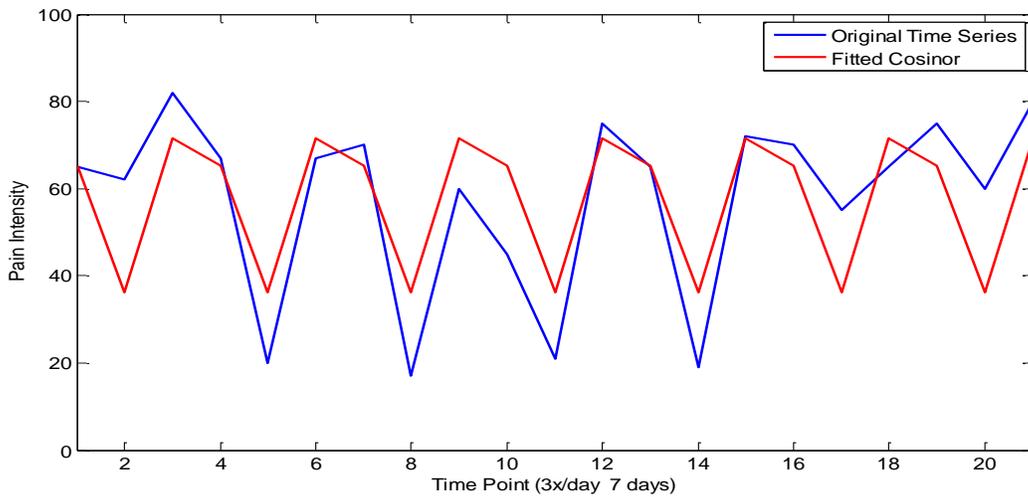


Figure 5-3c: A33 significant zero amplitude ($p=0.03$), mesor=73.0, amplitude=48.0, morning acrophase

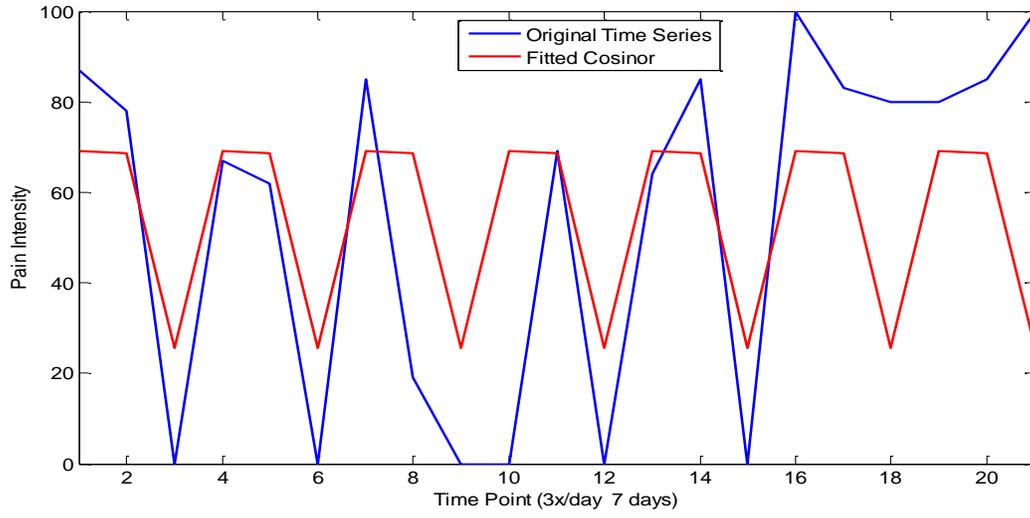


Figure 5-3d: B22 significant ($p=0.01$), mesor=4.1, amplitude=4.3, morning acrophase

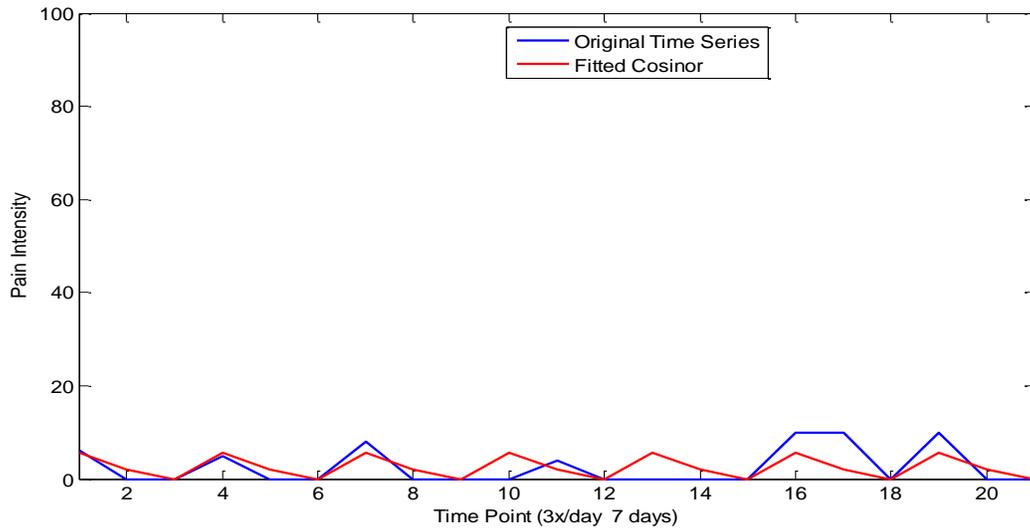


Figure 5-3e: A11 non-significant zero amplitude ($p=0.44$), mesor=22.1, amplitude=10.5

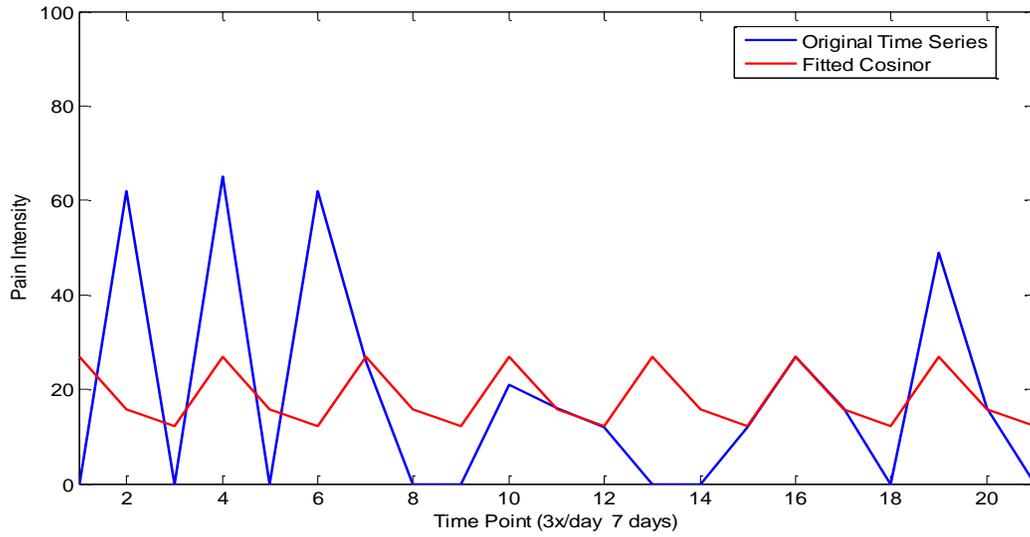


Figure 5-3f: A26 non-significant zero amplitude ($p=0.63$), mesor=53.2, amplitude=7.2

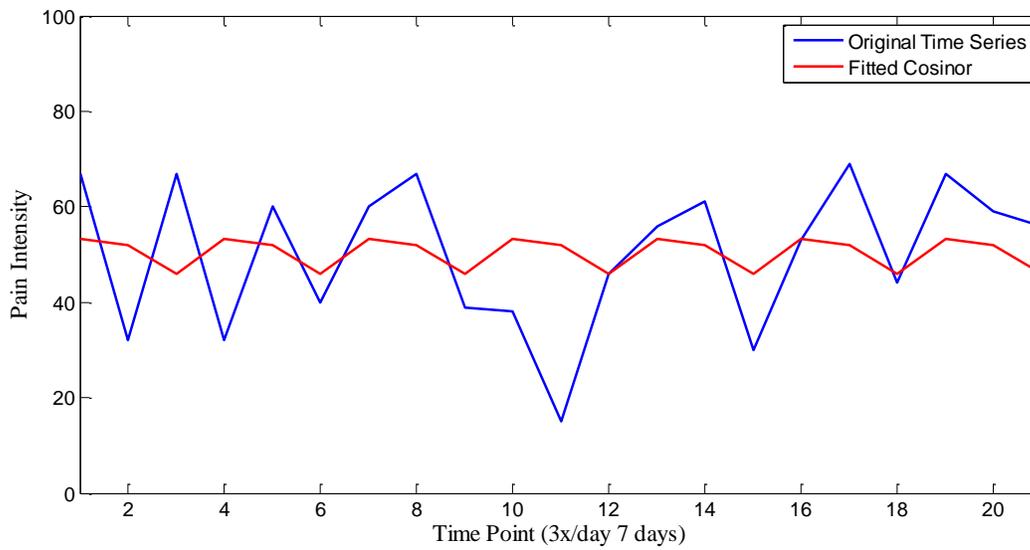


Figure 5-3g: A42 non-significant zero amplitude ($p=0.44$), mesor=43.3, amplitude=16.0

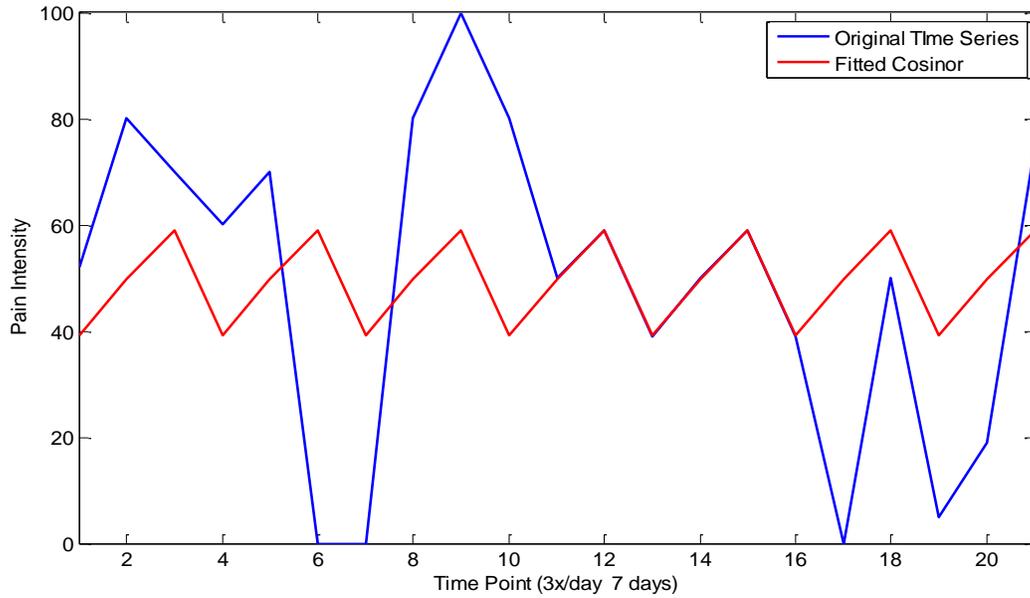


Figure 5-3h: A44 non-significant zero amplitude ($p=0.67$), mesor=77.1, amplitude=7.4

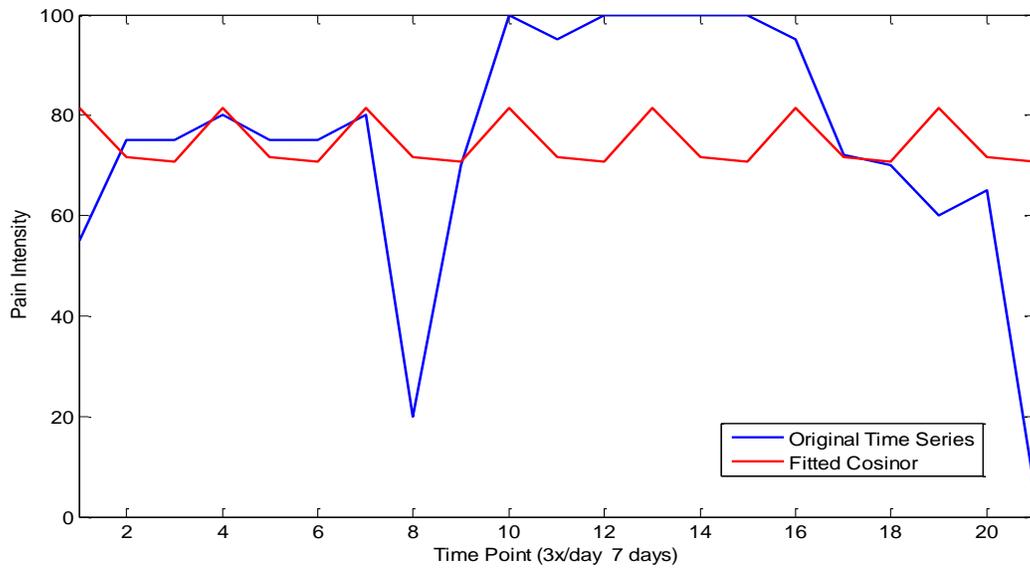
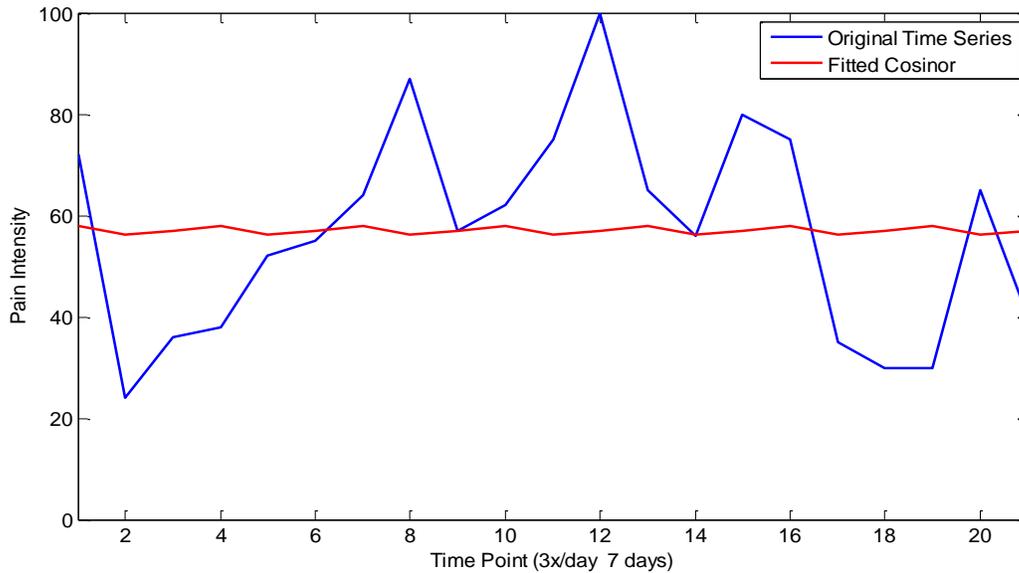


Figure 5-3i: A04 non-significant ($p=0.99$), mesor=57.2, amplitude=0.9



In Table 5-5 the proportion of significant zero amplitude tests from the cosinor analyses is compared between the full imputed dataset ($n=85$), a dataset containing only cases with at least six days of full data ($n=23$) and a dataset containing only cases with at least five days of full data ($n=54$) to compare the effect of missingness on the proportion of significant cosinor analyses. Restricting analysis to only those cases with minimal imputations (at least 6 days of full data) produces the highest proportion of significant cosinor analyses, although there is only minimal change with the larger datasets. The non-imputed dataset ($n=85$) is used in GEE analysis; therefore, cosinor analysis results from the large dataset are presented. This produces more conservative cosinor analysis results.

Table 5-5: Comparison of cosinor analysis results between full and reduced datasets

	Proportion of Cosinor Analyses (%)		
	Significant ($p < 0.05$)	Borderline ($0.05 < p < 0.10$)	Non-significant ($p > 0.10$)
Full Dataset n=85	22.4	7.1	70.6
Cases with ≥ 5 days full data n=57	24.1	5.6	70.4
Cases with ≥ 6 days full data n=26	26.1	0.0	73.9

n = number

Cosinor analysis on Monte Carlo simulation with bootstrapping

Cosinor analyses were conducted on 1000 similar sized simulated matrices computed from the original dataset using Monte Carlo bootstrapping sampling methods. A proportion of significant ($p < 0.05$) cosinor analyses was produced for each matrix of 85x21 data points, resulting in 1000 proportions. The proportions of significant zero amplitude tests from the cosinor analyses of the simulated data ranged from 0 to 14.1% with an average proportion of 5.0%. The proportion of significant zero amplitude test from the imputed dataset (n=85) was 22.4% which is outside of the range produced in the simulated dataset, indicating that the proportion found in the clinical dataset exceeds what would be found by chance alone.

5.1.7 Logistic Regression

The following variables were tested on univariate analysis for inclusion in the full model of logistic regression (Objective 1.2): age, sex, diagnosis, PGADS, disease duration and total number of active joints. Table 5-6 shows the results of the univariate analysis. Age, diagnosis, PGADS and total number of active joints had p values less than 0.25 and were therefore retained for the full model. The p value for sex exceeded the 0.25 criterion; however, it was considered a biologically relevant variable and was therefore retained for the full model. P values for total

number of active joints and disease duration exceeded 0.25 and were therefore not considered for the full model.

Table 5-6: Study 1 results of univariate analysis for logistic regression

Variable	Wald Chi-Square	df	Sig.	Decision
Age	1.83	1	0.18	Include - $p < 0.25$
Sex	0.25	1	0.62	Include - biologically relevant
Diagnosis (4 categories)	3.36	3	0.07	Include - $p < 0.25$
Disease Severity (PGADS)	2.26	1	0.13	Include - $p < 0.25$
Disease Duration	0.53	1	0.47	Exclude - $p > 0.25$

PGADS = Physician Global Assessment of Disease Severity (0-100)

Sig. = significance

df = degrees of freedom

In the full model, PGADS exceeded the criterion ($p < 0.05$) for inclusion and was therefore removed from the final model. Although age also exceeded the criterion, it was retained in the final model for biological significance. The final model included age, sex and diagnosis. Table 5-7 shows the results of the logistic regression.

Table 5-7: Study 1 logistic regression full model results

Variable	$\hat{\beta}$ [S.E.($\hat{\beta}$)]	$e^{\hat{\beta}}$	p value	95% CI OR	
				Lower Bound	Upper Bound
Sex	0.918 [0.693]	2.5	0.185	0.64	9.75
Age	0.281 [0.136]	1.3	0.039*	1.01	1.73
Psoriatic, enthesitis and other (reference category)			0.057		
Systemic onset	2.460 [1.071]	11.7	0.022*	1.44	95.46
Oligoarticular	1.914 [1.016]	6.8	0.060	0.93	49.70
Polyarticular RF+ and RF-	0.731 [0.942]	2.1	0.438	0.33	13.16
Constant	-6.486 [2.213]	0.0	0.003		

Sex reference category = female

* significant at $p=0.05$ level

The test statistic for the logistic regression is the likelihood ratio test (LRT).

$$\text{LRT} = [-2\text{Log likelihood reduced model}] - [-2\text{Log likelihood full model}]$$

LRT is compared to a χ^2 distribution with k degrees of freedom where k=number of additional variables in the model. The reduced model included only age and sex and had a $-2LL=87.88$. The full model had k=3 extra variables (diagnosis) and had a $-2LL=79.30$. Therefore $\text{LRT}=8.58$, which is compared to a χ^2 distribution with 3 degrees of freedom (7.82). Since the $\text{LRT} (8.57) >$ the critical $\chi^2_3 (7.82)$ the LRT exceeds the criterion for significance at the 95th percentile. The addition of diagnosis categories to a model including age and sex is a significant model.

Logistic regression interpretation

Both age and diagnosis predicted the probability of having a significant cosinor analysis. With each increased year of age, youth had increased odds (OR=1.3, 95% CI OR= 1.01, 1.73, $p=0.039$) of having a statistically significant cosinor analysis. In other words, as children get older, they are more likely to have systematic variability in their pain intensity. With a five year increase in age there is a 4.1 increased odds of having systematic variability (cosine rhythm) in pain intensity. The confidence interval for age is narrow and therefore precise.

Compared to youth with psoriatic, enthesitis or other arthritis, youth with systemic arthritis had 11.7 times greater odds of having a significant cosine rhythm to pain intensity ($p=0.022$) (Table 5-7). Oligoarticular arthritis subtype had a borderline ($p=0.06$) but non-significant increased odds of having a significant cosinor analysis compared to youth with psoriatic, enthesitis or other arthritis. Youth with polyarticular arthritis (RF+ or -) did not have an increased odds of having a significant cosine rhythm in pain intensity compared to those with psoriatic, enthesitis or other arthritis. However, all of the 95% confidence intervals for the parameter estimates of the diagnostic subgroups were very wide. The low number of participants in each diagnostic category contributed to the imprecision of these estimates. Post-hoc power analysis revealed that a sample size of approximately 157 participants would be needed to achieve a power of 80% given the change in R^2 of 0.19 observed in the regression with the addition of diagnostic categories.

5.1.8 Generalized Estimating Equations

Correlations were examined within the pain intensity matrix to determine which working correlation matrix to use in the model. There was no structure to the correlations. An unstructured working correlation matrix did not converge; therefore an independent working correlation matrix was selected for all GEEs. ⁽¹⁷⁵⁾ Cumulative logits were modeled on ordinal logistic models with pain as a categorical variable. The following variables were tested on univariate analysis for consideration for inclusion in the full model: sex, age, diagnosis, disease duration, disease severity, and TOD (Table 5-8).

The results of the univariate analysis for two cut-points for pain categorization were compared (See section 4.1.4.3.1 and Table 4-1 for descriptions and decision rules). The parameter estimates did not differ more than 20 percent between the two strategies; therefore,

strategy 1 was selected as the pain categorization cut-points since this resulted in a more even distribution of pain scores across categories.

Sex, and age were included in the GEE model (Objective 1.3) even though the p values exceeded the 0.25 criterion because they were considered potentially relevant for interaction analysis and because diagnosis and age were predictive variables in the logistic regression following cosinor analysis. Disease duration, diagnosis and TOD were included in the full model based on the screening criterion. Disease severity was excluded from the full model based on the screening criterion.

Table 5-8: Study 1 results of univariate analysis for GEE

Variable	Pain Cut-Point Strategy 1		Pain Cut-Point Strategy 2		df	Decision
	β	Sig.	β	Sig.		
Sex	0.27	0.370	0.25	0.422	1	Include – biologically relevant
Age	-0.01	0.932	-0.01	0.879	1	Include – biologically relevant
Disease Duration	0.04	0.216	0.04	0.245	1	Include – $p < 0.25$
Diagnosis (1st category)	0.72	0.088	0.71	0.089	3	Include – $p < 0.25$
Disease Severity (PGADS)	0.01	0.255	0.01	0.265	1	Exclude – $p > 0.25$
Time of Day (1st category)	0.20	0.065	0.02	0.060	2	Include – $p < 0.25$

PGADS - physician global assessment of disease severity
Sig. - significance

df - degrees of freedom

In the full model no variables were found to be significant ($p < 0.05$) on examination of the parameter estimates; therefore disease duration was removed from the final model. Age, sex, diagnosis and TOD were retained for examination of interactions because they were important predictors on the logistic regression following cosinor analysis (age, diagnosis), biologically relevant variables for interaction analysis (sex), or central to the research question (TOD).

The following interactions were examined in the full model inclusive of interactions:

1. TOD by diagnosis; to determine if time of day effects on pain differ by diagnostic subtype
2. TOD by sex; to determine if time of day effects on pain differ by sex
3. TOD by age; to determine if time of day effects on pain differ by age

In a model containing the interactions TOD by diagnosis, TOD by sex and TOD by age, the TOD by diagnosis and TOD by sex were significant predictors of pain intensity. The final model included main effects of sex, diagnosis and TOD and interactions TOD by diagnosis and TOD by sex. Age was not a significant predictor as a main effect or in an interaction and was therefore removed from the final model for parsimony.

Interpretation of the GEE results is by comparison of the proportional odds of the responses between subgroups. Figures 5-4a to 5-4h plot the predicted probabilities of each pain category by time of day for males and females to present the interaction of TOD and sex. Figures 5-5a to 5-5h plot the predicted probabilities of each pain category by time of day for each diagnostic category to present the interaction of TOD and diagnosis. It is critical to note that the y-axes of each of the graphs differ in range. Comparisons are only to be made within graphs; therefore the y-axes that most clearly display the results have been selected. Since all main effects were involved in significant interactions, interpretation will only be made on the interactions.

GEE Interpretation

Pain intensity varies systematically throughout the day for youth with JIA and the pattern of fluctuation varies by subgroup of disease and by sex. For interpretation, 95% confidence intervals for the predicted probabilities of occurrence of each of the four pain categories are compared in the following manner:

1. within sex, between TOD
2. between sex, within each TOD
3. within diagnosis, between TOD
4. between diagnosis, within each TOD

5.1.8.1.1 Within sex, between TOD

For both males and females, the 95% CIs for predicted probabilities do not overlap at any time of day for all four pain categories (see Figures 5-4a to 5-4h) indicating that differences in probabilities are statistically significant. Females have a significantly higher probability of having no pain in the afternoon than both other times of the day ($\beta=0.50$; 95% CI=0.07, 0.92; OR=1.7; $p=0.02$), whereas males have a significantly higher probability of having no pain in the evening compared to morning or afternoon. For females, the probability of having moderate or severe pain is highest in the morning, drops slightly in the afternoon and rises again in the evening. Males have a significantly higher probability of having moderate or severe pain in the morning and this probability declines throughout the day.

5.1.8.1.2 Between sex, within TOD

Males have a significantly higher probability than females of having no pain in the morning and evening. The 95% CIs for probability of having no pain overlap for males and females in the afternoon; therefore, there is no difference between sexes in the probability of having no pain in the afternoon. Females have a significantly higher probability of having mild pain in the evening than males. In the morning and afternoon males and females do not differ in their probability of having mild pain. Females have a significantly higher probability of having moderate or severe pain in the evening than males. There is minimal to no difference in the probability of having moderate to severe pain at both other times of day for males and females.

5.1.8.1.3 Within diagnosis, between TOD

For all four diagnostic categories, the 95% CIs for predicted probabilities do not overlap at any time of day for all four pain categories (see Figures 5-5a to 5-5h) indicating that differences in probabilities are statistically significant. For systemic onset, oligoarthritis and both polyarticular arthritis RF+ and RF-, there is a significantly higher probability of having no pain

in the afternoon ($\beta=0.67$; 95% CI = 0.10, 1.25; OR=2.0; $p=0.02$), whereas mornings have the highest probability of having moderate or severe pain. The pattern is opposite for youth with psoriatic, enthesitis-related or other arthritis for whom the probability of having no pain is highest in the evening and the probability of having moderate or severe pain is greatest in the afternoon.

5.1.8.1.4 Between diagnosis, within TOD

Probability of having no pain at each time of day is lowest in youth with systemic arthritis. Youth with oligoarthritis have the highest probability of having no pain in the afternoon and youth with enthesitis-related arthritis, psoriatic arthritis or other arthritis have the highest probability of having no pain in the morning or evening. Youth with systemic arthritis have the lowest probability of having mild pain in the morning compared to other diagnostic groups and youth with psoriatic, enthesitis or other arthritis have the lowest probability of having mild pain in the evening compared with other diagnostic groups. Youth with systemic arthritis have the highest probability of having moderate or severe pain at all times of day. Youth with oligoarthritis have the lowest probability of having moderate or severe pain in the afternoon. Youth with psoriatic, enthesitis or other arthritis have the lowest probability of having moderate or severe pain in the morning and evening compared to other diagnostic groups.

Figure 5-4: Predicted Probabilities of Pain Categories by Time of Day and Sex

Figure 5-4a: Probability of No Pain for Females and Males

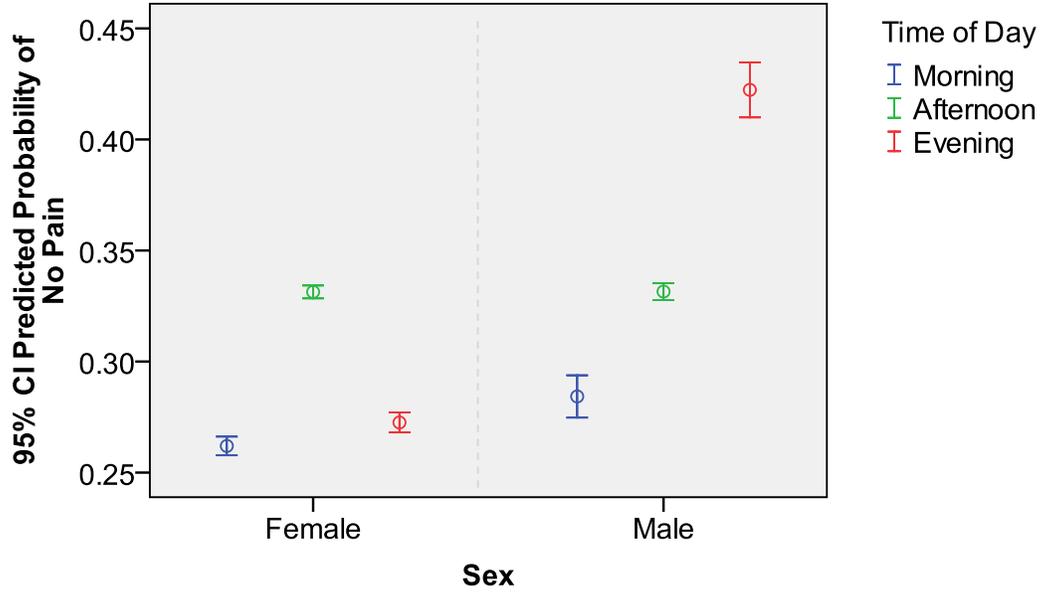


Figure 5-4b: Probability of Mild Pain for Females and Males

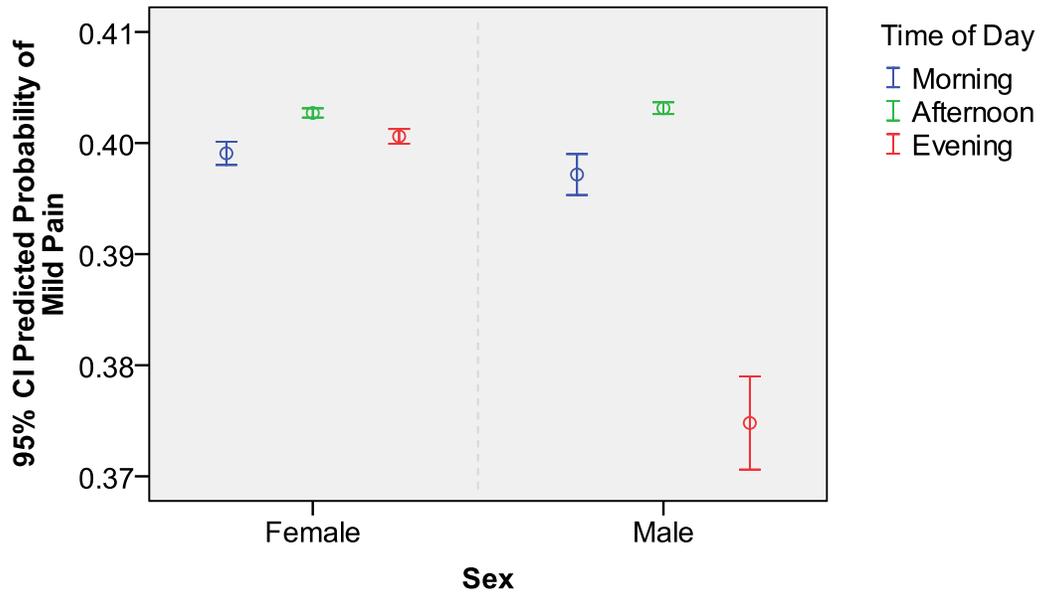


Figure 5-4c: Probability of Moderate Pain for Females and Males

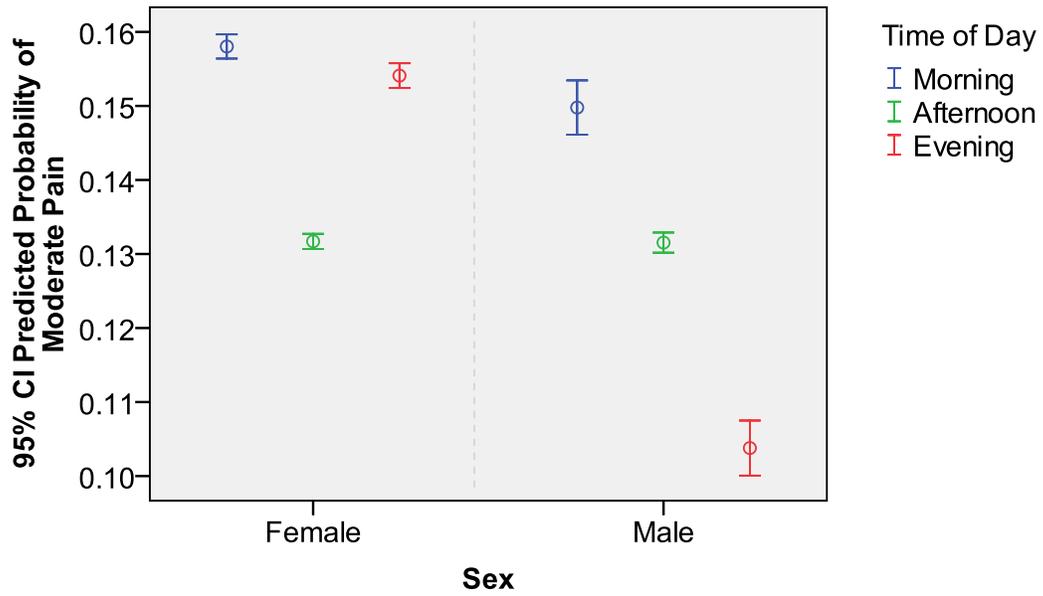


Figure 5-4d: Probability of Severe Pain for Females and Males

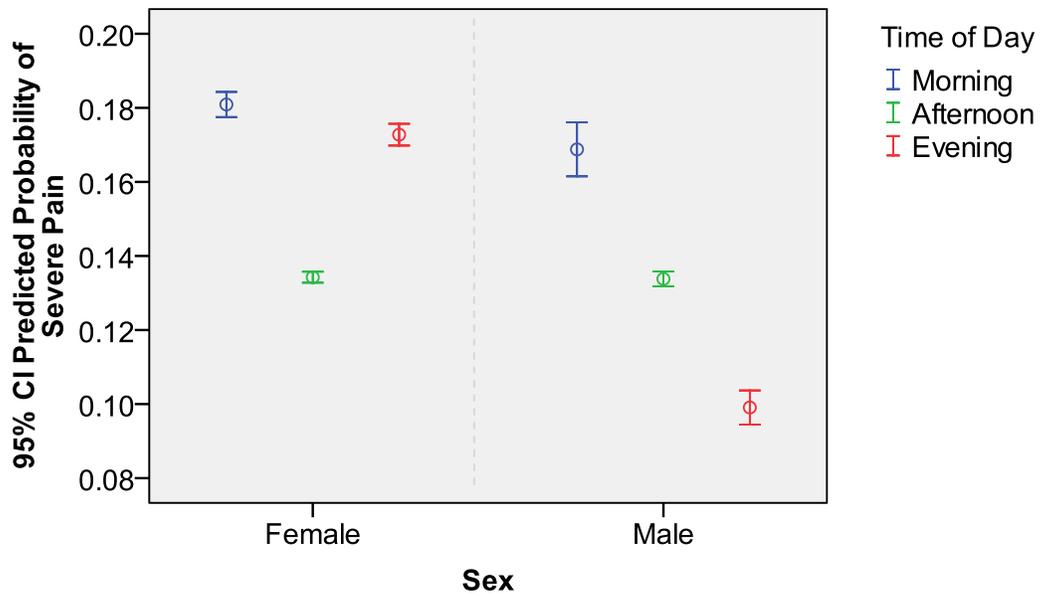


Figure 5-4e: Probability of No Pain by Time of Day

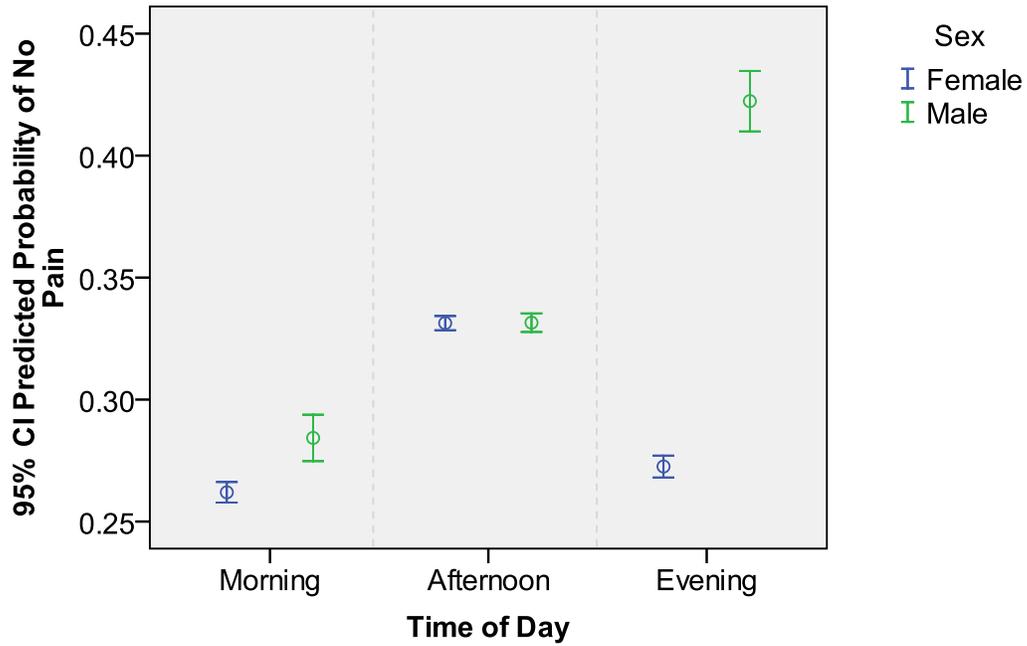


Figure 5-4f: Probability of Mild Pain by Time of Day

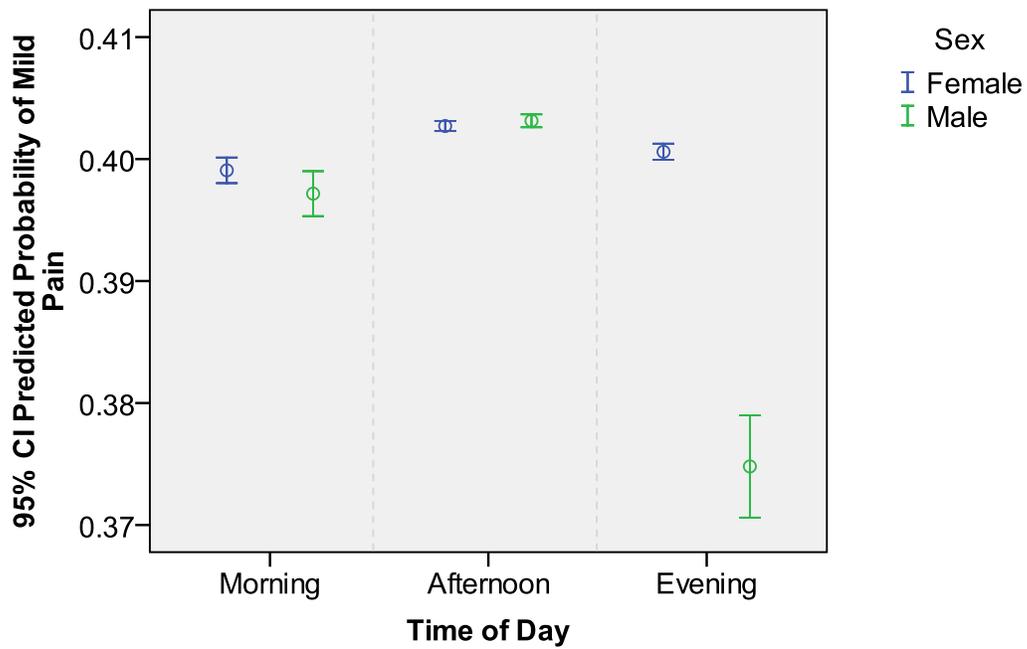


Figure 5-4g: Probability of Moderate Pain by Time of Day

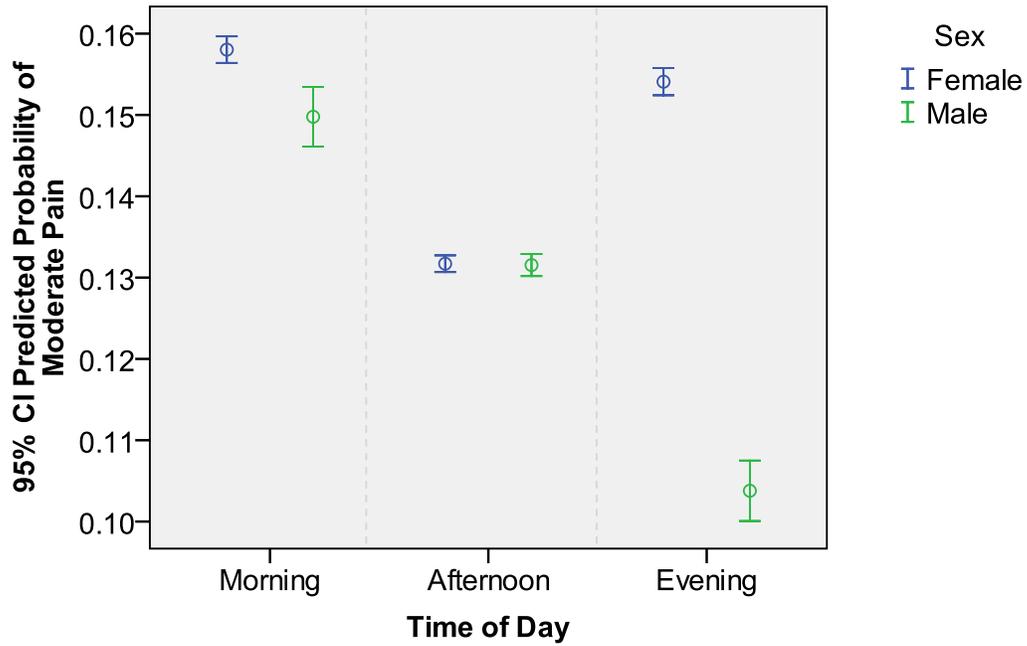


Figure 5-4h: Probability of Severe Pain by Time of Day

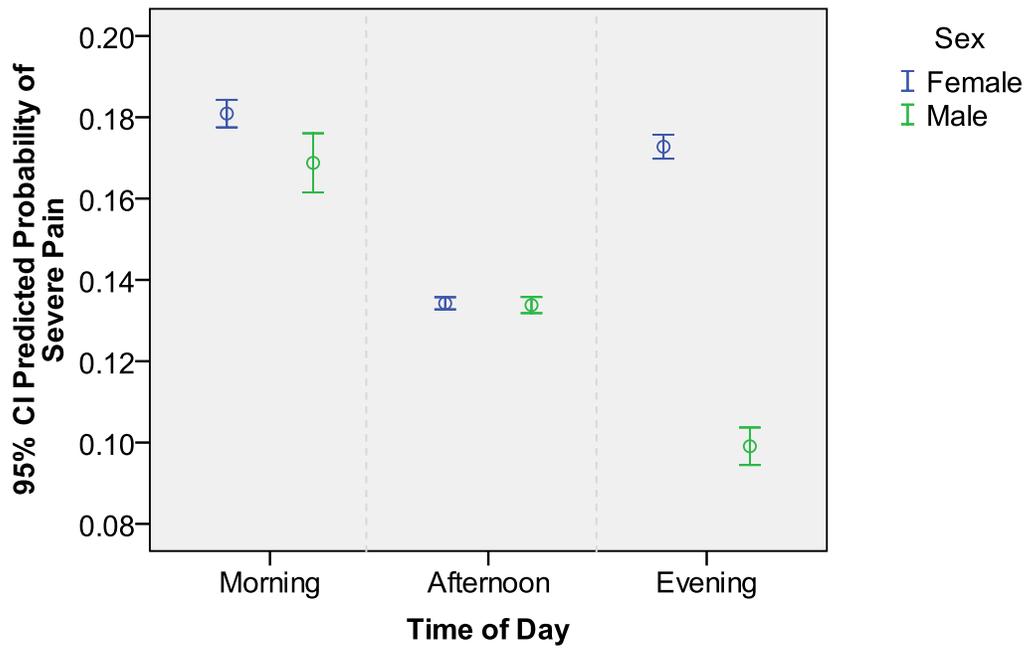


Figure 5-5: Predicted Probabilities of Pain Categories by Time of Day and Diagnosis

Figure 5-5a: Probability of No Pain by Diagnosis

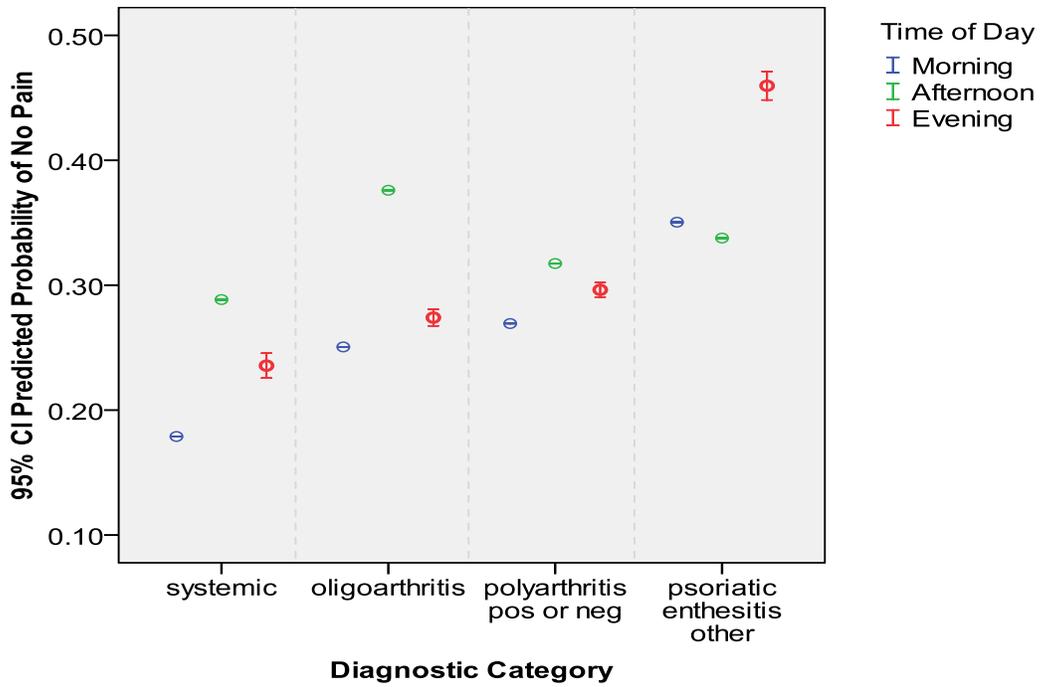


Figure 5-5b: Probability of Mild Pain by Diagnosis

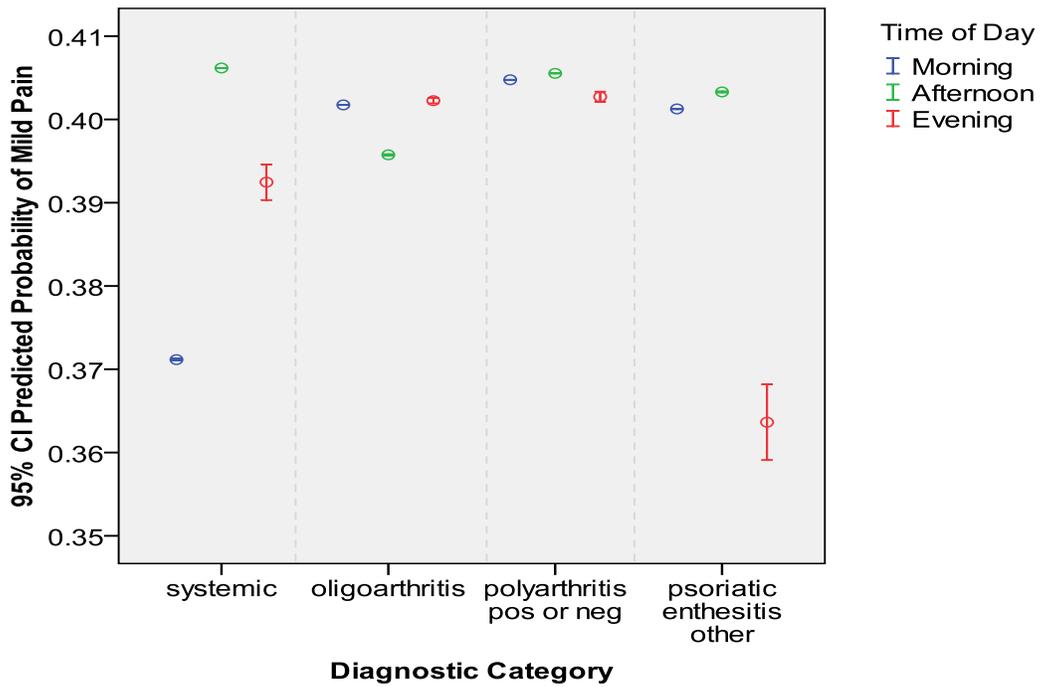


Figure 5-5c: Probability of Moderate Pain by Diagnosis

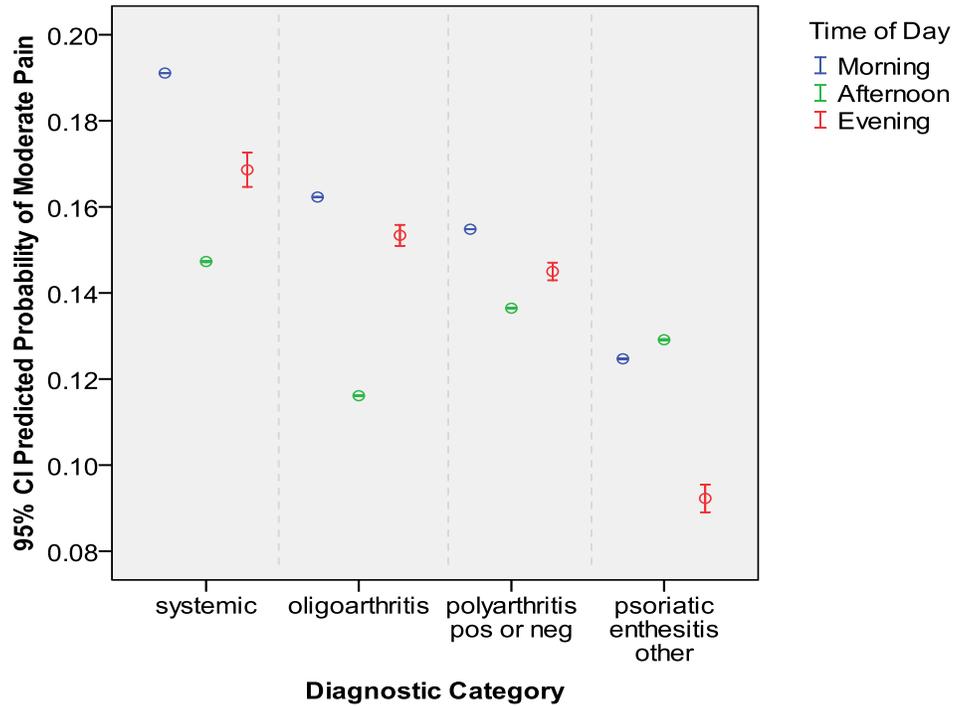


Figure 5-5d: Probability of Severe Pain by Diagnosis

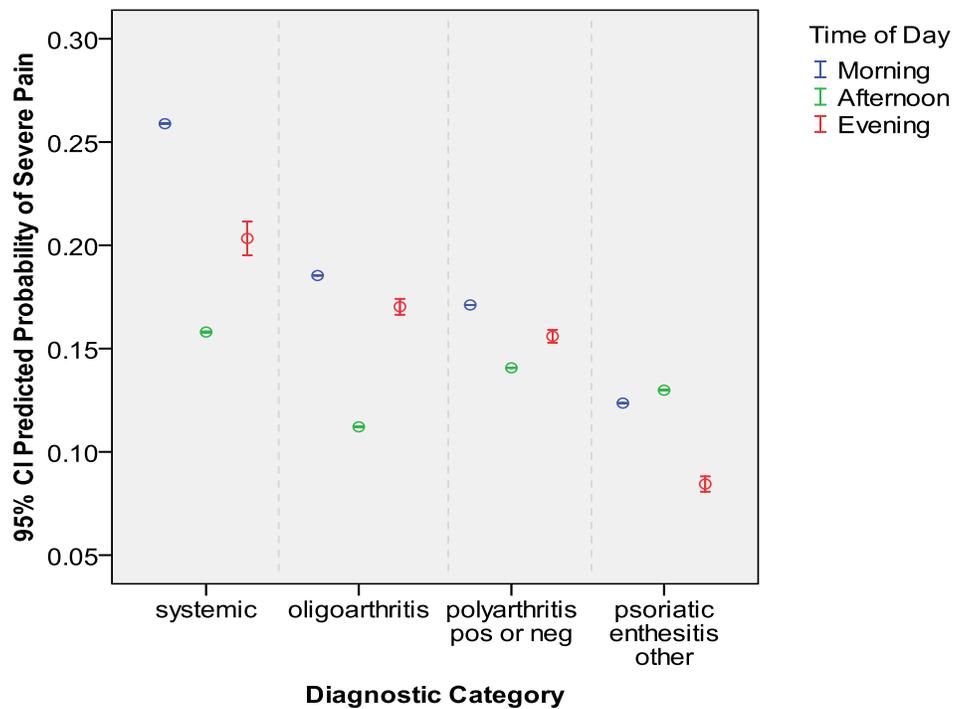


Figure 5-5e: Probability of No Pain by Time of Day

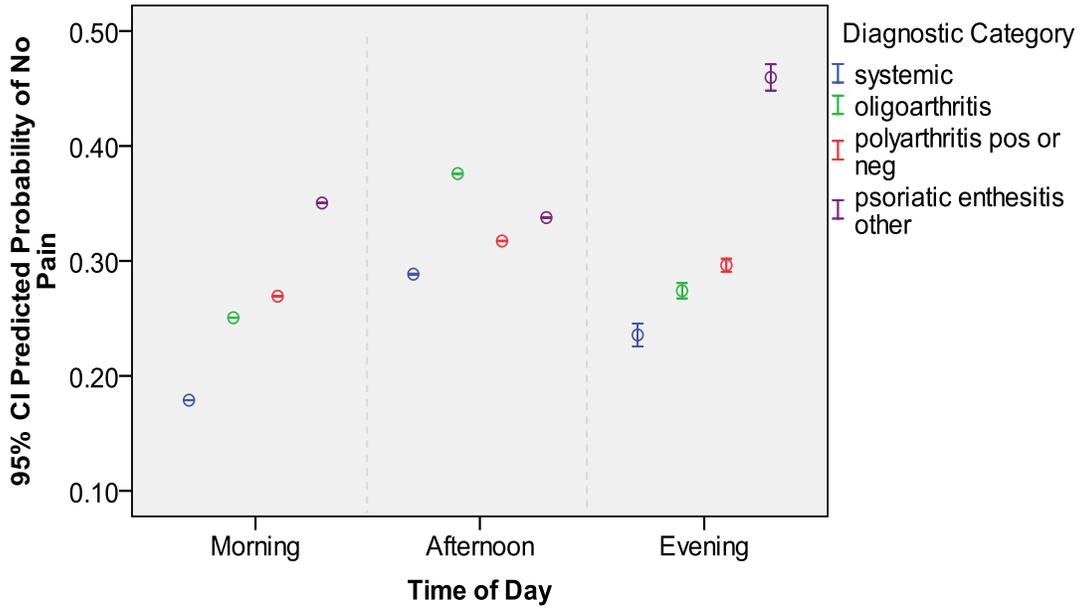


Figure 5-5f: Probability of Mild Pain by Time of Day

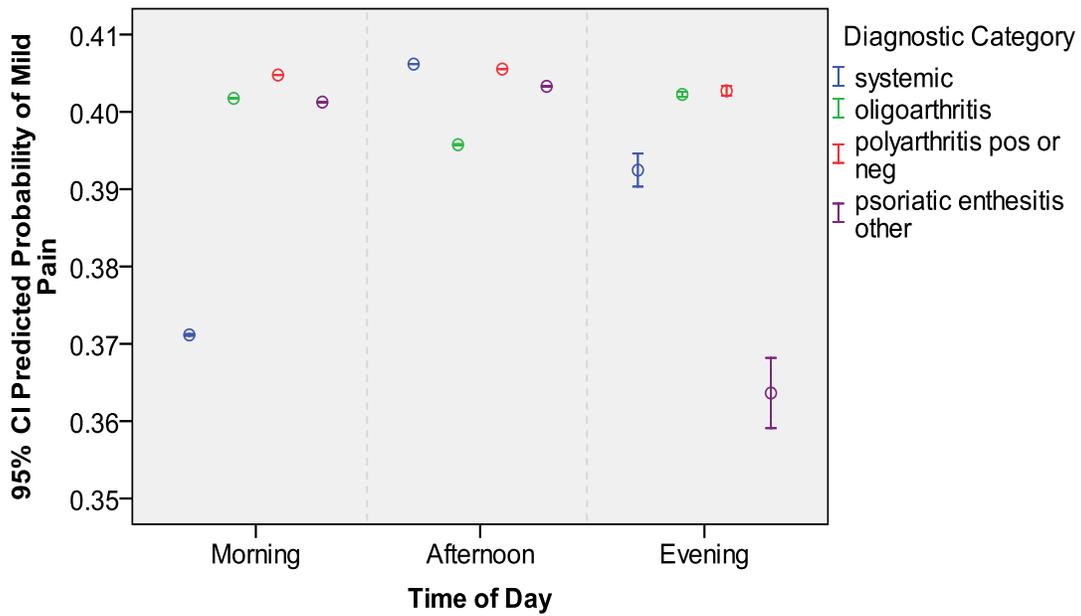


Figure 5-5g: Probability of Moderate Pain by Time of Day

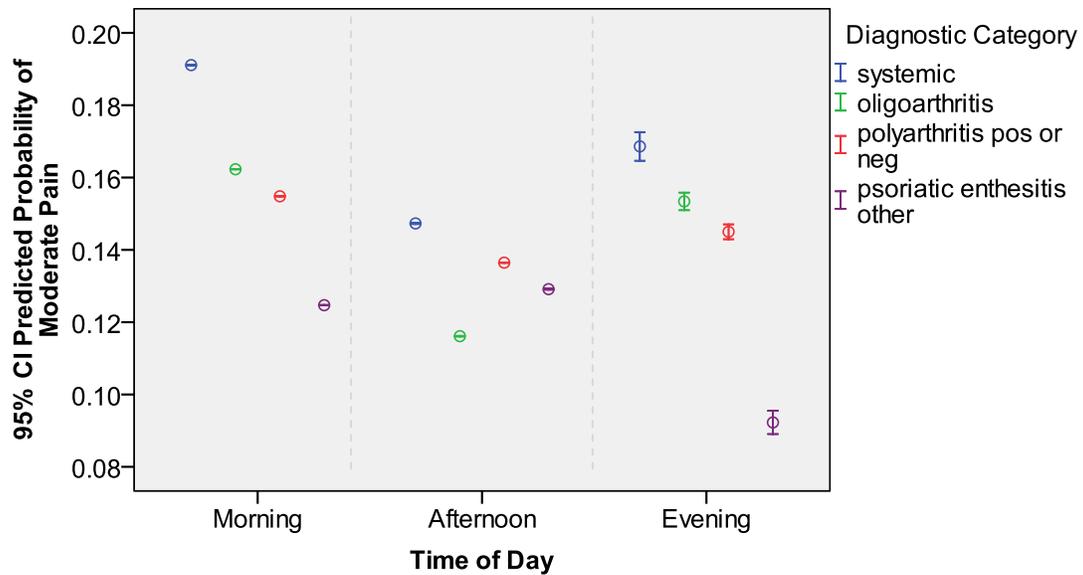
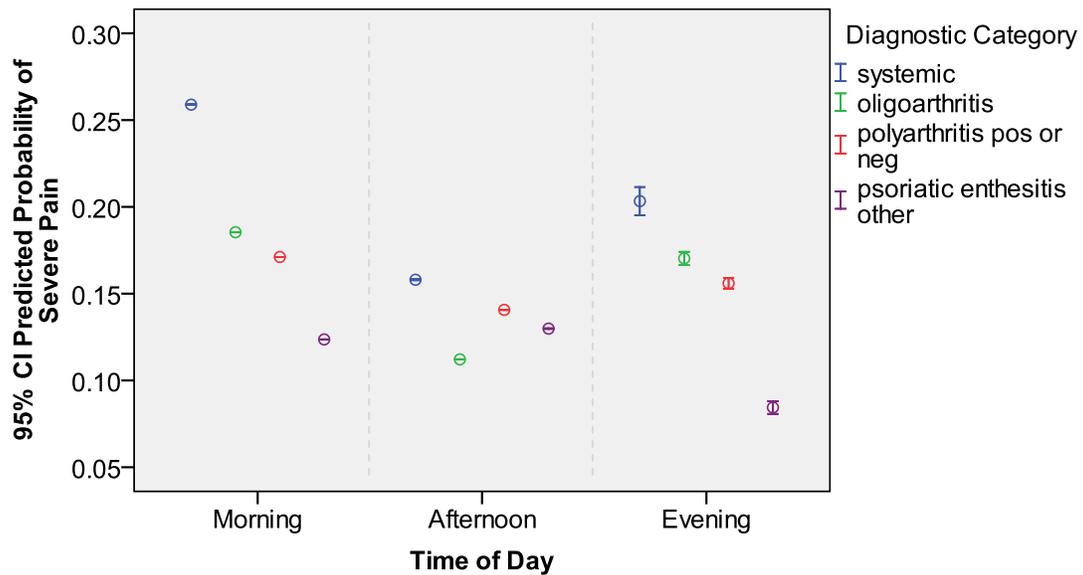


Figure 5-5h: Probability of Severe Pain by Time of Day



5.2 Study 2: Explaining within-day variability of pain in youth with JIA and non-arthritic persistent pain

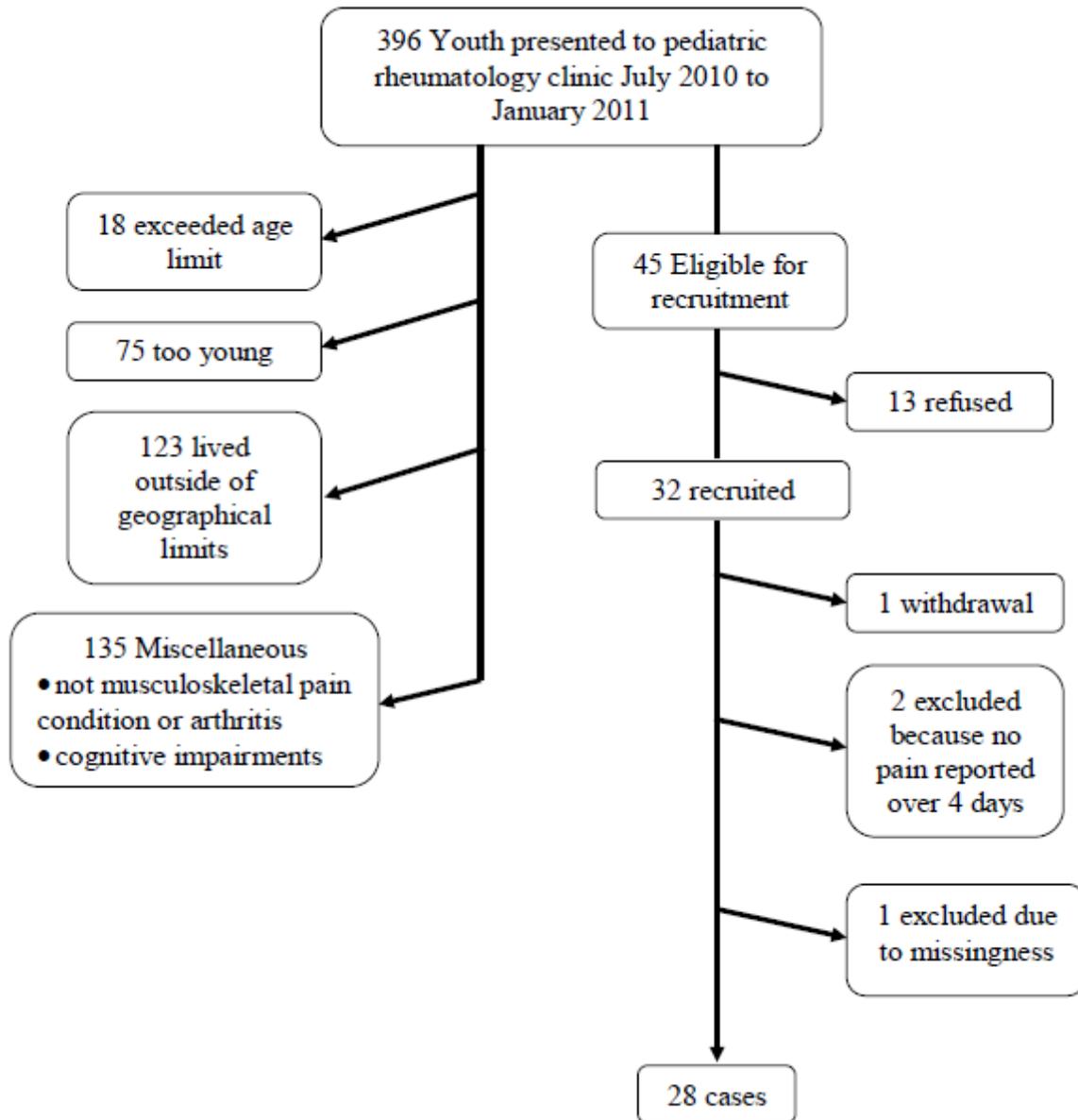
5.2.1 Data Management

Data for Study 2 collected by electronic diary on the PInGo app were uploaded from the Rackspace server web-page to a Microsoft Excel data file where they were converted from comma delimited format and then translated to SPSS for cleaning and analysis. Data from questionnaires and clinical data collection forms were directly entered into an SPSS 17.0 data file. Both the electronic diary data and questionnaire data for each participant were checked twice for accuracy of entry. Individual participant files were merged into a single working dataset that was analyzed in SPSS version 17.0. At the group level, data were checked for range, distribution and outliers to further verify data accuracy.

5.2.2 Sample

Patients meeting the study criteria who presented for a clinical appointment between July 7, 2010 and January 10, 2011 were invited to participate in the study. Participant recruitment is presented in a flow diagram in Figure 5-6. Of the 396 patients who presented to the rheumatology clinic during the recruitment phase, only 45 were eligible for recruitment. The majority of youth were ineligible for recruitment because they presented to the clinic with a complaint other than arthritis or a pain condition or lived outside of a two hour driving radius of Saskatoon, SK. Thirteen ($13/45 = 28.9\%$) youth refused to participate, with the primary reason cited as being too busy. One participant withdrew following consent but prior to data collection ($1/45 = 2.2\%$). The reason provided for withdrawal was a busy schedule. None of the youth recruited were excluded from the study based on inability to understand the electronic diary.

Figure 5-6: Study 2 Participant Flow Diagram



Data from two individuals were not used in analysis because pain was not reported over the four day period ($2/45 = 4.4\%$). Data from the remaining 29 cases were examined for completeness. In the entire dataset diary entries were missing on 56 occasions (6.9%). Individual rates of missingness ranged from 0 to 10 occasions (35.7%) over the four day study protocol.

The individual with 10 missing diary entries was excluded from analysis based on the criteria for missingness, leaving a final sample of 28 participants ($28/45 = 62.2\%$).

The mean age of youth recruited for Study 2 was not significantly different than those in Study 1; however, youth in Study 1 had a significantly longer disease duration than those in Study 2 ($t=2.2$, $df=109$, $p=0.03$). There was a significantly higher proportion of males in Study 2 (60.7%) than Study 1 (27.1%) ($\chi^2=58.7$, $df=1$, $p<0.01$). Demographic characteristics could not be collected on youth who did not enrol; therefore it is difficult to interpret whether the higher proportion of males was representative of youth attending the clinic during the recruitment period, the inclusion criterion biased selection towards males, or females were more likely to refuse participation.

5.2.3 Demographic and disease characteristics

Mean age of participants was 14.1 (SD=2.2; range = 9.8 to 17.8), 61% were male and 86% were Caucasian. There were no statistically significant differences between JIA and non-JIA groups on any of the demographic or disease characteristics. Continuous variables were assessed with independent samples t-tests and categorical variables with Mann-Whitney U test. Demographic and disease characteristics of the participants are presented in Table 5-9.

Table 5-9: Study 2 participant demographic and disease characteristics

Characteristic (expected range)	Participants included in analysis		
	n = 28		
	n (%)	M (SD)	Range
Age (8 to 18 years)		14.1 (2.2)	9.8 to 17.8
Male	17 (60.7)		
Female	11 (39.3)		
Group			
JIA	11 (39.3)		
Non-JIA	17 (60.7)		
Race			
Caucasian	24 (85.7)		
Aboriginal	1 (3.6)		
Other	3 (10.7)		
Disease Duration (0 to 18 years) n=26		2.7 (3.8)	0.0 to 17
PHV (-5 to +5) n=26		+ 0.6 (2.1)	-3.9 to 3.4
BMI (healthy = 19-25) n=28		22.3 (4.6)	15.7 to 34.2
PAQ (0 to 5) n=28		2.4 (0.6)	1.3 to 3.9
CHAQ (0 to 3) n=28		0.5 (0.4)	0.0 to 1.4
PedsQL (0 to 100) n=26		65.0 (14.5)	38.0 to 92.4
SES (8 to 66) n=27		44.4 (12.3)	25 to 66
ESR (normal <20mm/hr) n=17		12.1 (16.9)	2.0 to 72.0

n = number

% = percentage

M = mean

SD = standard deviation

PedsQL = pediatric quality of life questionnaire

SES = Hollingshead Index of Socioeconomic Status

PHV = peak height velocity

BMI = body mass index (healthy range = 20-25)

PAQ = physical activity questionnaire

CHAQ = childhood health assessment questionnaire

ESR = erythrocyte sedimentation rate

Youth recruited for Study 2 had a range of diagnoses. Of the 11 youth in the JIA group, there were no youth with systemic or oligoarticular arthritis, five youth had either polyarticular

RF+ or RF- JIA, and six youth had either enthesitis, psoriatic or undifferentiated subtypes of JIA. Of the 17 youth in the non-JIA group, four had idiopathic or musculoskeletal lower extremity pain, six had idiopathic polyarthralgia, four had idiopathic or musculoskeletal low back pain, and three had other localized pain conditions that will not be described in order to protect the anonymity of the participants.

Information on disease duration was not available for two participants (7.1%) since the date of diagnosis was not evident from the medical records. ESR values were not available for 11 participants (39.3%) since the test was not medically necessary and therefore not completed for those patients. No further analysis with the ESR values was conducted due to the high number of missing values. There was insufficient ethnic diversity within the sample to warrant further analysis based on ethnicity. The PedsQL was not available for two participants (7.1%). These participants lived out of town and mailed back the questionnaire packages with the PedsQL not completed. The Hollingshead SES score could not be completed for one participant. Therefore, family income and home ownership status were used as surrogate estimates of SES. SES was categorized into an ordinal variable with 3 categories based on the categorization of Hassan et al.⁽³⁰⁵⁾ Peak height velocity could not be calculated for two participants since their age exceeded the limits for computation of the test. As a result, PHV was dichotomized into pre/post PHV for analysis.

5.2.4 PInGo Data Quality

PInGo diary entries were examined to determine if time of day, demographic or disease characteristics were related to missingness. To account for correlation from repeated measures, a binary logistic GEE was run with an independent working correlation matrix. Missing diary entries was the dependent variable and age, sex, group and TOD were entered as main effects. Only age was a statistically significant predictor of missingness ($\beta=0.16$; 95% CI 0.04 to 0.29; $p=0.01$). With each five years of increased age, there was a 2.2 increase in the odds of missing a diary entry ($5 \times 0.16 = 0.8$; OR= 2.23). However, overall, the diary entry rates were excellent with only a very small percentage of missing entries (5.9%).

PInGo diary entries were also examined for delay of onset from the scheduled time of completion. The majority (74.4%) of entries were made within 15 minutes of the scheduled data

collection (range = 0 to 59 minutes). The mean delay from the scheduled time of completion was 10.2 minutes.

5.2.5 Pain Intensity Characteristics

Mean pain for the entire sample over the four days was moderate ($M = 34.9$; $SD = 28.4$; range 0-100). The median pain score was 32 (IQR=56), and the sample overall had a positive skew (0.26; $SE = 0.09$) and negative kurtosis (-1.2; $SE 0.18$). Of the 738 diary entries, 46 were missing (5.9%) and 176 were zero scores (22.4%). Individual mean pain intensities ranged from 4.0 ($SD = 7.6$) to 75.2 ($SD = 9.7$). JIA and non-JIA groups differed in pain reports with the JIA group reporting a significantly lower overall pain intensity (See Table 5-10), and a significantly higher proportion of zero scores. There was no significant difference in proportion of missing data between the two groups. Figures 5-7 and 5-8 are histograms of pain intensity distributions for the two groups.

Table 5-10: Study 2 pain intensity characteristics by group

	JIA n=294 N=11	Non-JIA n=444 N=17	Significance tests
Mean pain intensity (SD)	27.9 (24.5)	39.6 (29.8)	Unpaired $t=5.60$, $p<0.01$
Median pain intensity (IQR)	26 (45)	37 (54)	
Range	0 to 100	0 to 100	
Skewness (SE)	0.50 (0.14)	0.04 (0.12)	
Kurtosis (SE)	-0.73 (0.28)	-1.39 (0.23)	
Missing (%)	14 (4.5)	32 (6.7)	Fisher's exact $p=0.13$
Zero Pain Score Reported (%)	81 (26)	95 (20)	Fisher's exact $p=0.02$

n=number of diary entries completed
df = degrees of freedom

N= number of participants

Figure 5-7: Pain Intensity Distribution JIA Group

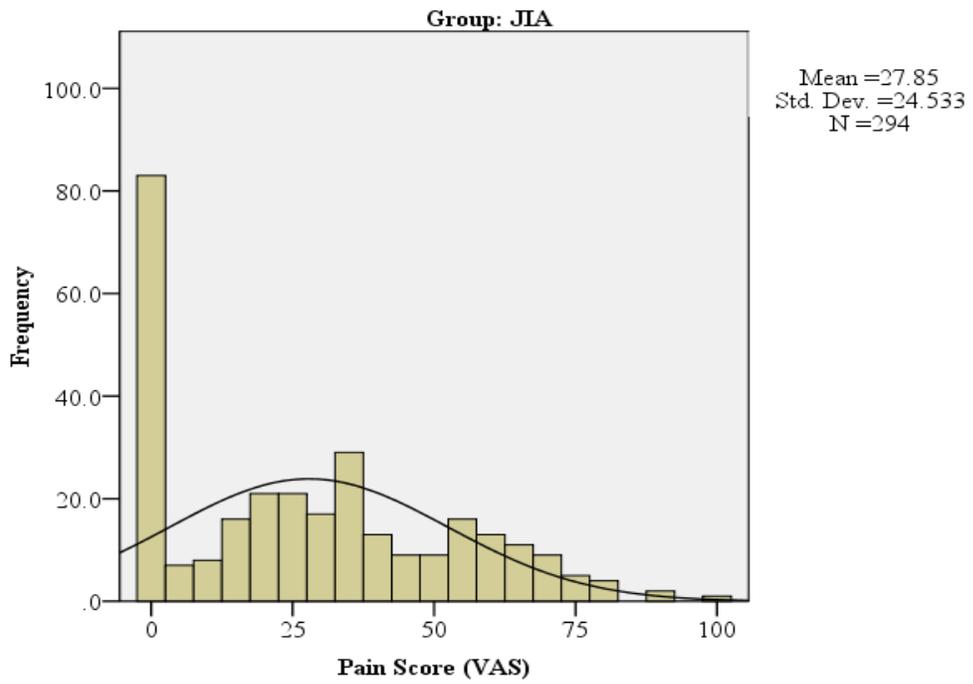
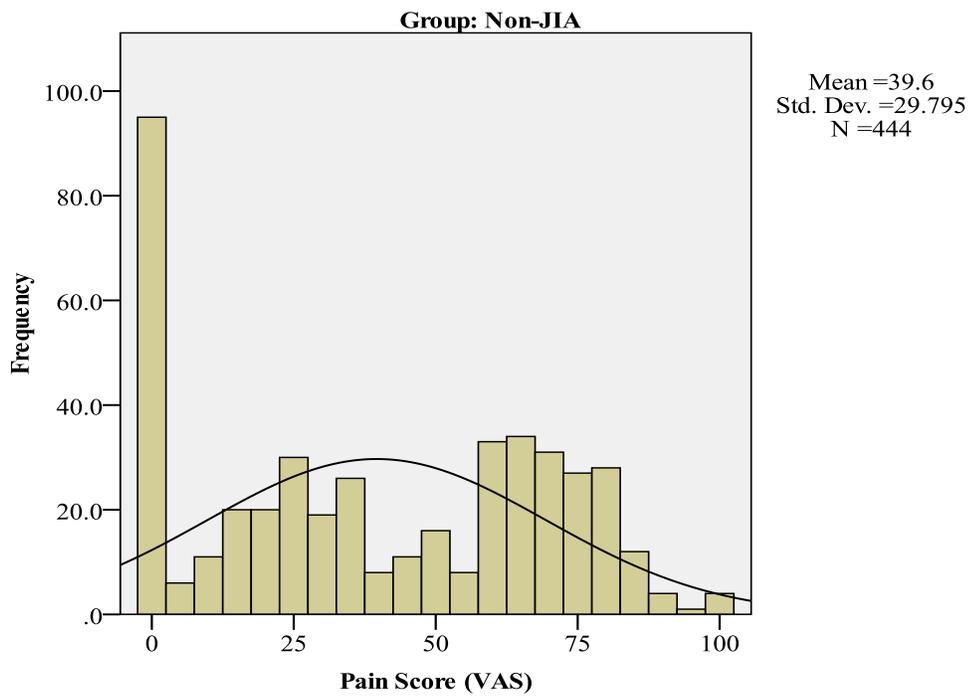


Figure 5-8: Pain Intensity Distribution Non-JIA Group



Both groups had similar Tweedie class distributions of pain intensity; therefore, pain intensity was transformed into an ordinal categorical variable for the GEE analysis. The same imputation method used in Study 1, TOD means, was used for imputation of missing data points for cosinor analyses. GEEs were computed with the non-imputed dataset.

5.2.6 Mood Data

Emotional activation and emotional valence scores were missing on 45 occasions (5.7%) from the entire sample. JIA and non-JIA groups differed significantly on emotional activation ($t=-6.16$, $p<0.001$, 95% CI=-18.77, -9.69). Frequencies of emotional valence categories and mood categories are presented in Table 5-11. Overall, youth with JIA reported higher emotional activation and a higher frequency of positive mood than youth in the non-JIA group.

Table 5-11: Mood characteristics by group

	JIA n=294 N=11	Non-JIA n=444 N=17	Total n=738 N=28
Mean emotional activation (SD)	61.3 (30.5)	47.1 (30.9)	52.7 (31.5)
Proportion of Emotional Valence Categories			
Negative or Neutral	25.0	40.5	34.4
Positive	70.5	52.1	59.8
Missing Data (%)	4.5	6.5	5.7
Proportion of Mood Categories			
Low Valence/High Activation	12.3	15.8	14.4
Low Valence/Low Activation	12.7	24.8	20.0
High Valence/Low Activation	26.0	28.6	29.2
High Valence/High Activation	44.5	24.4	34.2

n=number of diary entries completed

N= number of participants

5.2.7 Cortisol Data

Saliva samples were missing on 17 occasions (7.6%) from the entire sample. Mean cortisol concentration was 38.1 ng/ml (SD=17.3, range=0 to 95.5) in the morning and 17.3 ng/ml (SD=13.4, range=0 to 73.3) in the evening. The majority of participants (89.3%) had a normal diurnal cortisol profile according to the criteria of Smyth et al. ⁽³³⁾ Only three participants had a flattened cortisol profile; therefore, no further analysis was conducted with the cortisol profile information due to insufficient heterogeneity.

5.2.8 Accelerometer Data

Overall, the majority (77.9%) of accelerometry windows had the full 120 minutes of wear. Wear minutes were regarded as missing if the accelerometer was worn for less than 84 minutes ($84/120 = 70\%$) during the two hour window. Based on this criterion, 17.7% of accelerometer windows were missing. In order to capture physical activity behaviour, including both activity and sedentariness, accelerometry data was converted into a categorical variable based on the quartiles of minutes of MVPA and sedentary minutes. Quartiles of minutes of MVPA and sedentary minutes are presented in Table 5-12.

Table 5-13 depicts how activity was categorized with frequencies of each activity category. Since only two windows were coded as high active/high sedentary, this category was collapsed and combined with the high active/low sedentary category, leaving three final activity categories. These categories represent three distinct patterns of activity. High active/low sedentary represents a higher intensity window of activity in which the participant is mostly lightly active with an accumulation of moderate to vigorous activity in excess of 11.3 minutes over the duration of the window. Low active/high sedentary represents a low intensity window of activity in which the participant is mostly sedentary, accumulating less than 11.3 minutes of MVPA. Low active/low sedentary represents a window of activity in which the participant is engaging primarily in light activity but not accumulating greater than 11.3 minutes of MVPA or greater than 90.5 minutes of sedentary activity. Overall, just under half of the activity windows (49.6%) were in the low active/low sedentary category.

Table 5-12: Quartiles of minutes of moderate to vigorous physical activity and sedentariness in accelerometry windows

	Sedentary Minutes	MVPA Minutes
Percentiles 25	47.1	0.8
50	73.4	3.5
75	90.5	11.3
Minimum	0.0	0.0
Maximum	116.3	62.3

MVPA - moderate to vigorous physical activity

Table 5-13: Categorization and frequency of activity levels

		Minutes of MVPA	
		< 75 th Percentile (%)	≥ 75 th Percentile (%)
Sedentary Minutes	≥ 75 th Percentile (%)	Low Active High Sedentary (24.6)	High Active High Sedentary ⁵ (0.3)
	< 75 th Percentile (%)	Low Active Low Sedentary (49.6)	High Active Low Sedentary (25.5)

⁵ The High Active-High Sedentary category was collapsed and merged with the High Active-Low Sedentary category due to low frequencies.

To assess the construct validity of the activity categorization, the correlation between the PAQ score and the weighted mean activity level was examined. There was a moderate and statistically significant correlation ($r_s=0.42$; $p=0.025$) between self-reported physical activity levels and the three activity categories. This degree of correlation is similar to previously reported associations between the PAQ and accelerometry outputs such as minutes of MVPA. ⁽³¹²⁾

Accelerometry data were examined to determine if time of day, demographic or disease characteristics were related to missingness. To account for within subject correlation due to repeated measures, a binary logistic GEE was run with an independent working correlation matrix. With insufficient wear (wear counts less than 84 of the possible 120 minutes) as the dependent variable, age, sex, group and TOD were entered as main effects. Time of day was the only significant predictor of the probability of insufficient wear with 6:00 to 8:00 am being the time of day most likely to have insufficient wear minutes (morning $\beta=4.14$; 95% CI = 3.26 to 5.03; $p<0.001$). Activity logs were examined for reasons provided for removal of the accelerometer. Accelerometers were primarily removed for showering or bathing and for most participants this occurred in the morning during the 6:00 to 8:00 am period. To examine the relationship between physical activity and pain, GEEs were computed with all activity windows, including those with fewer than 84 minutes of wear and separate GEEs with only those activity windows exceeding 84 minutes of wear time in order to compare the effect of missing accelerometry data on the analysis. The results of this analysis will be described in the GEE section.

5.2.9 Cosinor Analysis

Seven of the 28 analyzed pain intensity time series (25.0%) had statistically significant zero amplitude tests on cosinor analysis ($p<0.05$); two of 11 participants from the JIA group and five of 17 participants from the non-JIA group (Objective 2.1). There were no borderline significant cosinor analyses. Table 5-14 shows the characteristics of the cosinor parameter estimates.

Table 5-14: Study 2 cosinor parameters

	Significant Cosinor ($p < 0.05$)	
	n=7	
Parameter	M (SD)	Range
Mesor (0-100)	44.1 (24.2)	10.9 to 64.3
Amplitude (0-100)	21.1 (13.1)	7.2 to 41.9

M = Mean

SD = Standard Deviation

Over half of the acrophase occurred in the morning (4/7=57%), one acrophase occurred in the afternoon and two in the evening. Many time series showed multiple peaks during the day. Time-plots of a selection of significant and non-significant cosinor analyses with high and low within-day variability are presented in Figures 5-9a to 5-9g to demonstrate the range of variability observed. Figures 5-9a and 5-9b demonstrate cosinor analyses with significant zero amplitude tests and high within-day variability (amplitude ≥ 10). Figure 5-9c demonstrates a significant zero amplitude test with low within-day variability (amplitude < 10). Figures 5-9d and 5-9e demonstrate high within-day variability that is non-significant and Figures 5-9f and 5-9g demonstrate low within-day variability that is non-significant.

Figure 5-9: Study 2 Time Plots with Fitted Cosine Curves

Figure 5-9a: A06 Significant zero amplitude ($p=0.01$), mesor=32.4, amplitude=26.7, acrophase=morning

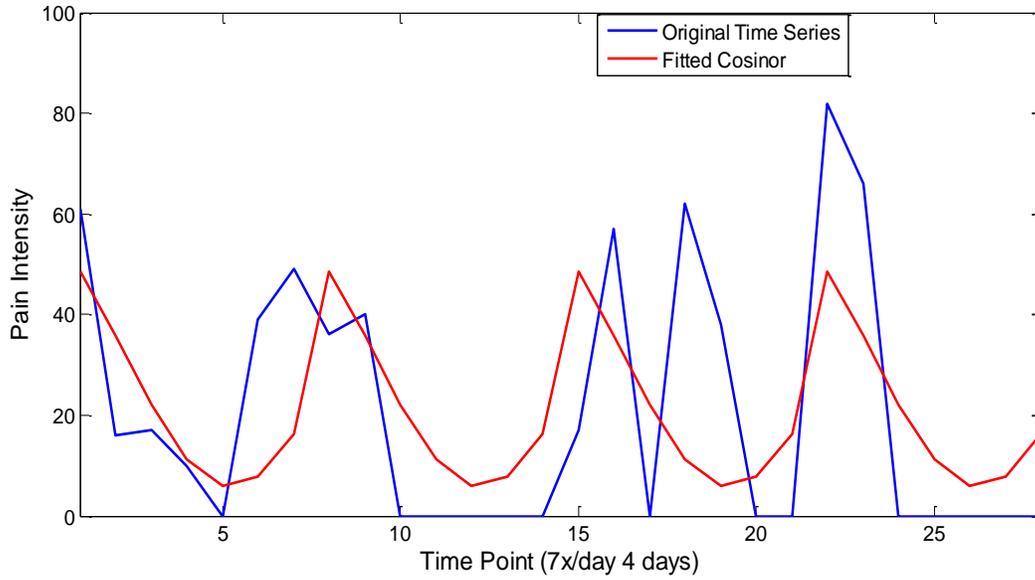


Figure 5-9b: B09 Significant zero amplitude ($p=0.01$), mesor=13.4, amplitude=32.3, acrophase=mid-afternoon

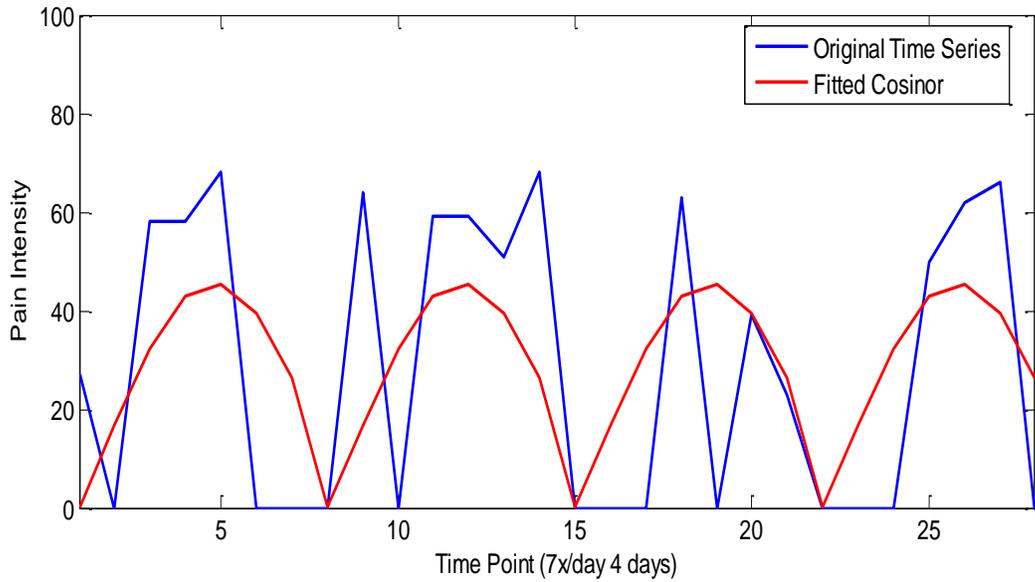


Figure 5-9c: B16 Significant zero amplitude ($p=0.04$), mesor=63.3, amplitude=7.2, acrophase=evening

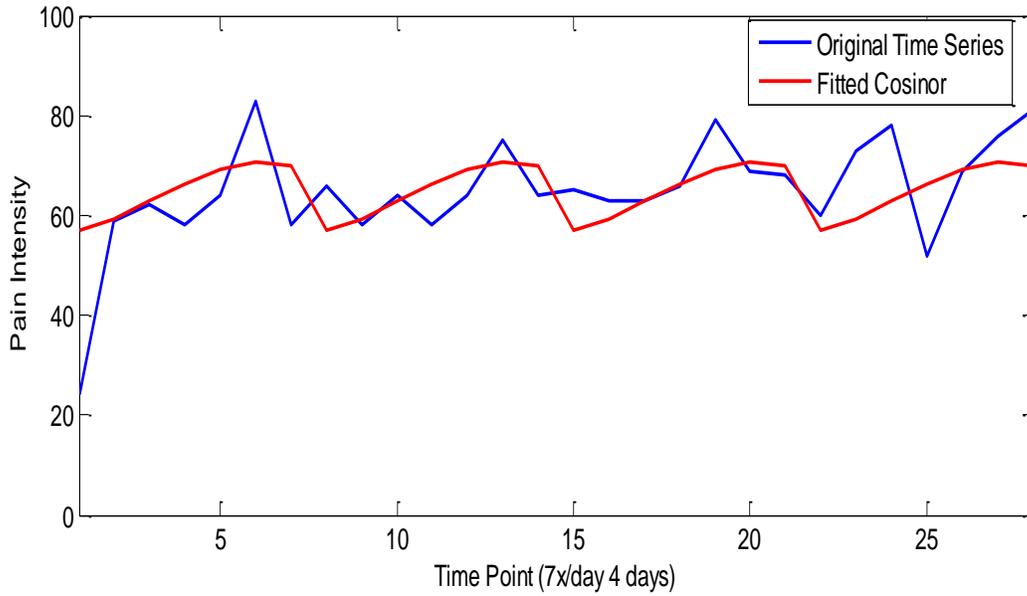


Figure 5-9d: A09 Non-significant zero amplitude ($p=0.23$), mesor=14.8, amplitude=20.6

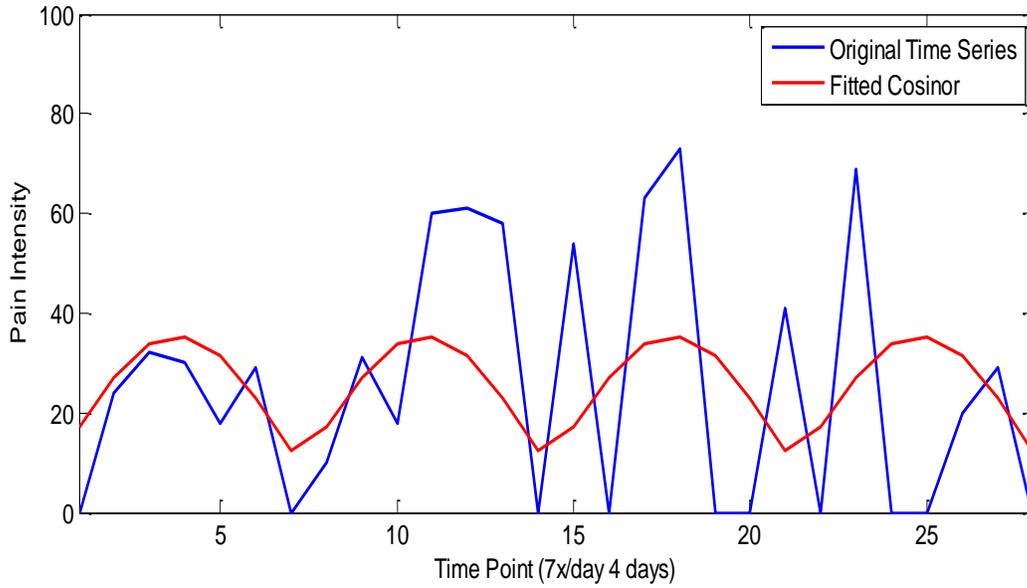


Figure 5-9e: B05 Non-significant zero amplitude ($p=0.16$), mesor=23.4, amplitude=20.4

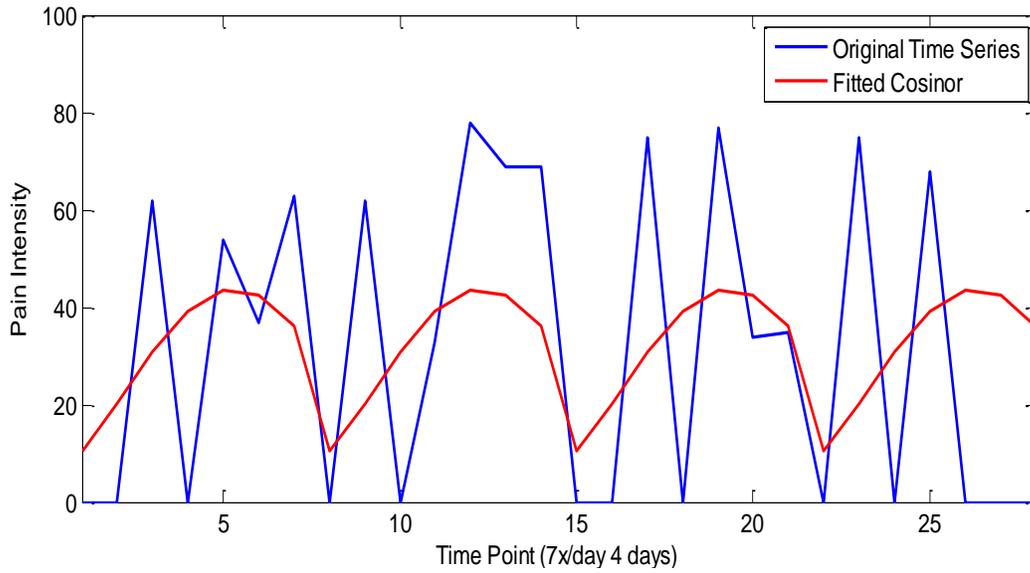


Figure 5-9f: B12 Non-significant zero amplitude ($p=0.58$), mesor=62.4, amplitude=6.5

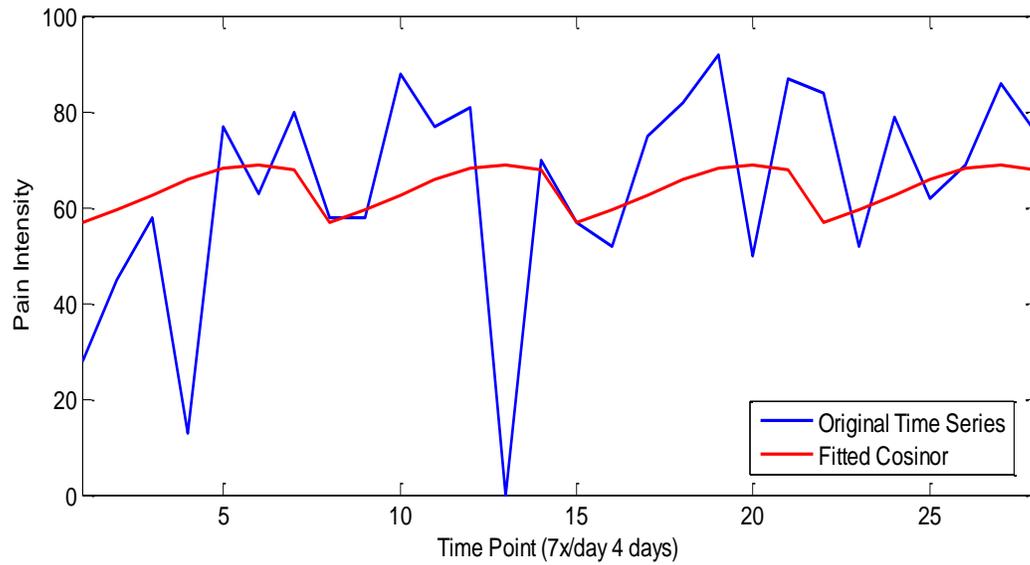
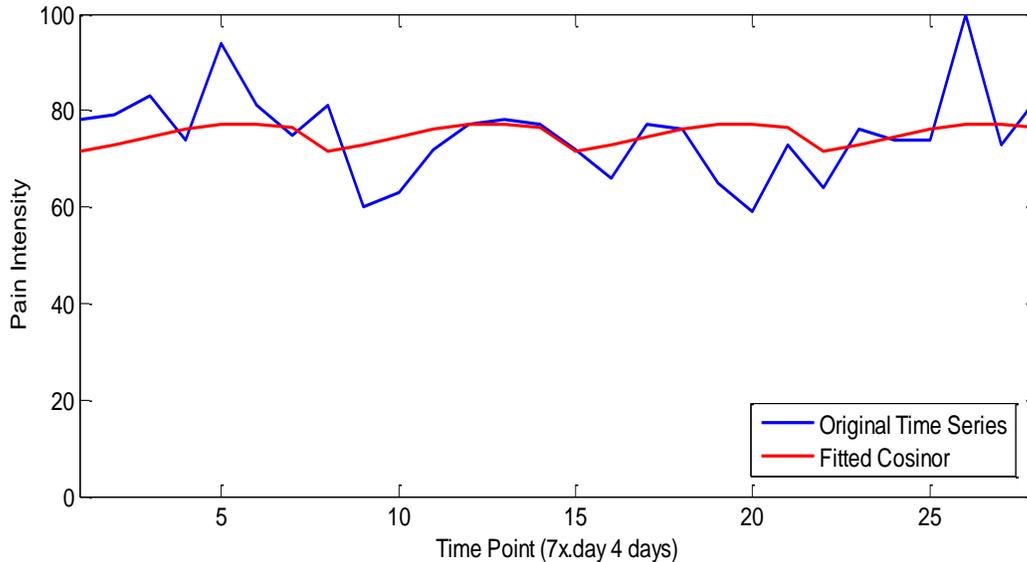


Figure 5-9g: B13 Non-significant zero amplitude ($p=0.46$), mesor=73.9, amplitude=3.4



Cosinor analysis on Monte Carlo simulation with bootstrapping

The proportion of significant zero amplitude tests in the resampled data (1000 matrices of 28x28) ranged from 0 to 23.3%, with an average proportion of 5.0%. The proportion of significant zero amplitude tests from the clinical dataset was 25% which is outside the range of that found in the simulated data and therefore exceeds what would be found by chance alone.

5.2.10 Logistic Regression

It is critical to note that according to the *a priori* sample size calculation, the logistic regression analysis for Study 2 had an insufficient sample size. Therefore, the confidence intervals were examined to determine precision of the estimates. The following demographic and disease variables were tested on logistic regression univariate analysis with significant zero amplitude test from cosinor analysis as the dependent variable: group, age, sex, BMI, disease duration, PAQ, CHAQ, PedsQL, pre/post PHV, SES category (Objective 2.2). Group ($p=0.53$) and sex ($p=0.82$) both exceeded the criterion for inclusion but were retained for the full model due to biological significance. Age ($p=0.25$) and CHAQ ($p=0.04$) were both retained for the full model based on the screening criterion.

The final model included age, sex, group and CHAQ as predictor variables. Table 5-15 displays the model parameter estimates from the logistic regression. CHAQ was a statistically significant predictor of the probability of having a significant zero amplitude test on cosinor analysis. Possible interactions between CHAQ and age, sex, group, PAQ, BMI, PHV, and disease duration were assessed; however, no statistically significant interactions were found. With each unit increase in CHAQ score, which represents a higher level of functional disability, there is a substantial increase in the odds of having systematic variability in pain intensity ($\beta=3.96$; OR=52.6; $p=0.03$). Age was borderline significant ($\beta=0.66$; OR=1.9; $p=0.10$). For each increased year of age, youth were more likely to have a significant zero amplitude test on cosinor analysis; however, this did not reach significance. However, all confidence intervals of the odds ratios were very wide, thus indicating imprecise estimates due to the insufficient power of the test. A general rule of thumb with logistic regression is that approximately 10 participants are needed for each independent variable included in the final model.^(153, 320) The results of this logistic regression should therefore be interpreted with extreme caution.

Table 5-15: Study 2 logistic regression of cosinor analysis outcomes

Variable	$\hat{\beta}$ [S.E.($\hat{\beta}$)]	$e^{\hat{\beta}}$	95% CI for EXP(β)		p value
			Lower	Upper	
Group	-1.600 [1.399]	0.2	0.01	3.14	0.253
Sex	-0.492 [1.406]	0.6	0.88	4.23	0.726
Age	0.656 [0.401]	1.9	0.04	9.61	0.102
CHAQ	3.963 [1.805]	52.6	1.53	1807.05	0.028*
Constant	-12.125 [6.258]	0.0			0.053

* significant at $p=0.05$ level

5.2.11 Generalized Estimating Equations

Correlations were examined within the pain response matrix to determine which working correlation matrix to use in the GEE analysis (Objective 2.3). There was no identifiable structure to the correlations. An unstructured working correlation matrix did not converge; therefore an independent working correlation matrix was selected for all GEEs.⁽¹⁷⁵⁾ Cumulative logits were modeled on ordinal logistic models with pain as a categorical variable. GEEs were first computed with the full dataset, then with a reduced dataset that included only the activity windows that had greater than 70% wear time. The following time-invariant disease and demographic variables were tested on univariate analysis first with the combined dataset (JIA and non-JIA groups combined): group, age, sex, BMI, disease duration, PAQ, CHAQ, SES and maturation. The following time-varying variables were tested on univariate analysis: TOD, total body areas in pain, mood, activity. Table 5-16 shows the results of the univariate analysis upon which subsequent models were built. To examine the effect of missing physical activity data (<70% wear time) on analysis, results of the univariate analysis were compared between the full dataset which included all activity windows and a reduced dataset which included only those windows with greater than 70% wear time. Since there was only minimal change in the parameter estimates (<20% change in β values) on univariate analysis between the full and reduced datasets, further analysis was conducted on the full dataset. Of the activity windows with less than 70% wear time, 94.9% were coded as light activity (low active/low sedentary) and 5.1% were coded as active (high active, low sedentary). Since participants reported that the most common reason for removal of the accelerometer was for showering, it was considered appropriate to code missing values as a light level of activity.

Variables were retained as main effects in the model if they met the criterion of $p < 0.25$ on univariate analysis, or if they were recognized as biologically important variables for further examination in interactions. On assessment of cell frequencies, the highest activity level was found to occur on only three occasions in the morning (6:00 to 8:00 am). Therefore, TOD cells were collapsed into four categories in the following manner: morning= 6:00am to 10:00am, during school=10:00 to 2:00pm, after school= 2:00pm to 6:00pm, evening=6:00 to 8:00pm.

Table 5-16: Study 2 results of univariate analysis for GEE (combined JIA and non-JIA data)

	Variable	Sig. (Wald Chi ²)	Decision
Time-Invariant Variables	Group	0.08	✓
	Age	0.38	Relevant for assessment of interactions
	Sex	0.04	✓
	BMI	0.17	✓
	Disease Duration	0.13	✓
	PAQ	0.34	Eliminate
	CHAQ	0.36	Eliminate
	PHV	0.11	✓
	SES	0.72	Eliminate
Time-Varying Variables	TOD	0.07	✓
	Mood	<0.01	✓
	Total # body locations in pain	<0.01	✓
	Activity	0.41	Relevant for assessment of interactions

BMI = body mass index

CHAQ = childhood health assessment questionnaire

SES = socioeconomic status

✓ = variable met criterion of $p < 0.25$ for inclusion in full model

PAQ = physical activity questionnaire

PHV = peak height velocity

TOD = time of day

When a main effects model was fit with group, sex, BMI, maturation, TOD, mood, total body locations, age, disease duration and activity, BMI, disease duration and maturation all exceeded the criterion ($p < 0.05$) for retention in the final model and were therefore excluded from subsequent models. All other variables were kept either because they met the criterion (mood, total body locations), or because they were biologically relevant variables to be examined in

interactions (group, age, sex, TOD, activity). Interactions between TOD and group, TOD and sex, TOD and age, activity and group, activity and sex, and TOD and activity were examined separately with the main effects. Only TOD by activity was a significant interaction. Although age and sex were not significant as main effects or in interactions, they were retained in the final model because of biological significance and because they were identified as relevant predictors in the logistic regression of Study 1 and Study 2 cosinor analysis outcomes. The final model included the following main effects and interaction: TOD, activity, mood, total body locations in pain, age, sex, and TOD by activity.

There was sufficient data to examine up to 23 variable levels in a GEE analysis of the non-JIA group and up to 15 variable levels in a GEE analysis of the JIA group. Table 5-17 shows the results of the univariate analysis upon which subsequent models were built. For the JIA group a main effects model was fit with the following variables: age, sex, BMI, disease duration, PHV, TOD, mood, total # body locations in pain, and activity. Age, sex, TOD and mood did not meet the $p < 0.05$ screening criterion but were retained in the final model due to biological relevance or because they were central to the research question. BMI, disease duration and PHV were eliminated from the final model because they did not meet the screening criterion. Total # body locations in pain and activity both met the criterion and were retained in the final model. There was insufficient data to conduct any interaction analyses for the JIA group.

For the non-JIA group a main effects model was fit with the following variables: age, sex, disease duration, TOD, mood, total # body locations in pain, and activity. Age, sex and TOD did not meet the $p < 0.05$ criterion but were retained in the final model due to biological relevance or because they were relevant for interaction analysis. Mood, total # body locations in pain and activity all met the screening criterion and were retained for the final model. The interaction between TOD and activity was also included in the final model of the non-JIA group. Therefore, the JIA group and non-JIA groups had the same main effects in the final GEE models and differed only in the inclusion of the interaction between TOD and activity that was not included in the JIA group final model due to insufficient data for this analysis.

Table 5-17: Results of separate group univariate analyses

	Variable	JIA Group		Non-JIA Group	
		Sig. (Wald Chi ²)	Decision	Sig. (Wald Chi ²)	Decision
Time-Invariant Variables	Age	0.31	Biologically relevant	0.86	Biologically relevant
	Sex	0.21	✓	0.03	✓
	BMI	<0.01	✓	0.96	Eliminate
	Disease Duration	0.36	✓	0.04	✓
	PAQ	0.92	Eliminate	0.25	Eliminate
	CHAQ	0.01	Eliminate	0.45	Eliminate
	PHV	0.02	✓	0.90	Eliminate
	SES	0.88	Eliminate	0.42	Eliminate
Time-Varying Variables	TOD	0.01	✓	0.02	✓
	Mood	0.08	✓	0.13	✓
	Total # body locations in pain	<0.01	✓	<0.01	✓
	Activity	0.59	Relevant for assessment of interactions	0.41	Relevant for research question

BMI = body mass index

CHAQ = childhood health assessment questionnaire

SES = socioeconomic status

✓ = variable met criterion of $p < 0.25$ for inclusion in full model

PAQ = physical activity questionnaire

PHV = peak height velocity

TOD = time of day

Interpretation of the GEE results is by comparison of the proportional odds of the responses between subgroups. As for Study 1, the y-axes differ between graphs since comparisons are only made within graphs.

5.2.11.1 GEE Interpretation

5.2.11.1.1 Number of body locations in pain

The mean number of body locations in pain at a single time point was 2.70 (SD=2.69) and ranged from 0 to 14 out of a possible 23 body locations on the body map. Pain intensity is significantly related to the total number of body locations in pain ($\beta=0.75$; 95% CI 0.57, 0.93; OR=2.1; $p<0.001$). As the number of body locations in pain increases, so does the probability of having severe pain (Figure 5-10). The overall mean predicted probability of having severe pain is 24%; however, on occasions when 5 or more body locations are identified as painful the predicted probability of having severe pain increases to 76% and on occasions where 7 or more body locations are identified as painful, the predicted probability of having severe pain increases to 91%. The results were the same for the JIA and non-JIA groups, therefore the combined results are presented in graphical format.

5.2.11.1.2 Mood

Within-day variability in pain intensity is related to within-day variability of mood (Figure 5-11). Both emotional valence and emotional activation had significant influence on the pain intensity category. At times of high emotional valence, there was a significantly greater probability of having no pain compared with times of low valence ($\beta=0.72$; 95% CI =.01, 1.43; OR=2.1; $p=0.047$). The combination of high valence and high activation (highest mood category) was associated with the greatest probability of having no pain in comparison with all other mood categories ($\beta=1.16$; 95% CI =.37, 1.95; OR=3.2; $p=0.004$). Low emotional valence, regardless of level of activation was associated with a significantly higher probability of having any level of pain with higher probabilities of moderate and severe pain during times of low valence, low activation ($\beta=0.95$; 95% CI =0.13, 1.78; OR=2.6; $p=0.023$). There were no significant differences in the probabilities of any of the four pain categories during times of high valence, low activation. The results were the same for the JIA and non-JIA groups, therefore the combined results are presented in graphical format.

Figure 5-10: Predicted Probability of Pain Category by Total Number of Body Locations in Pain

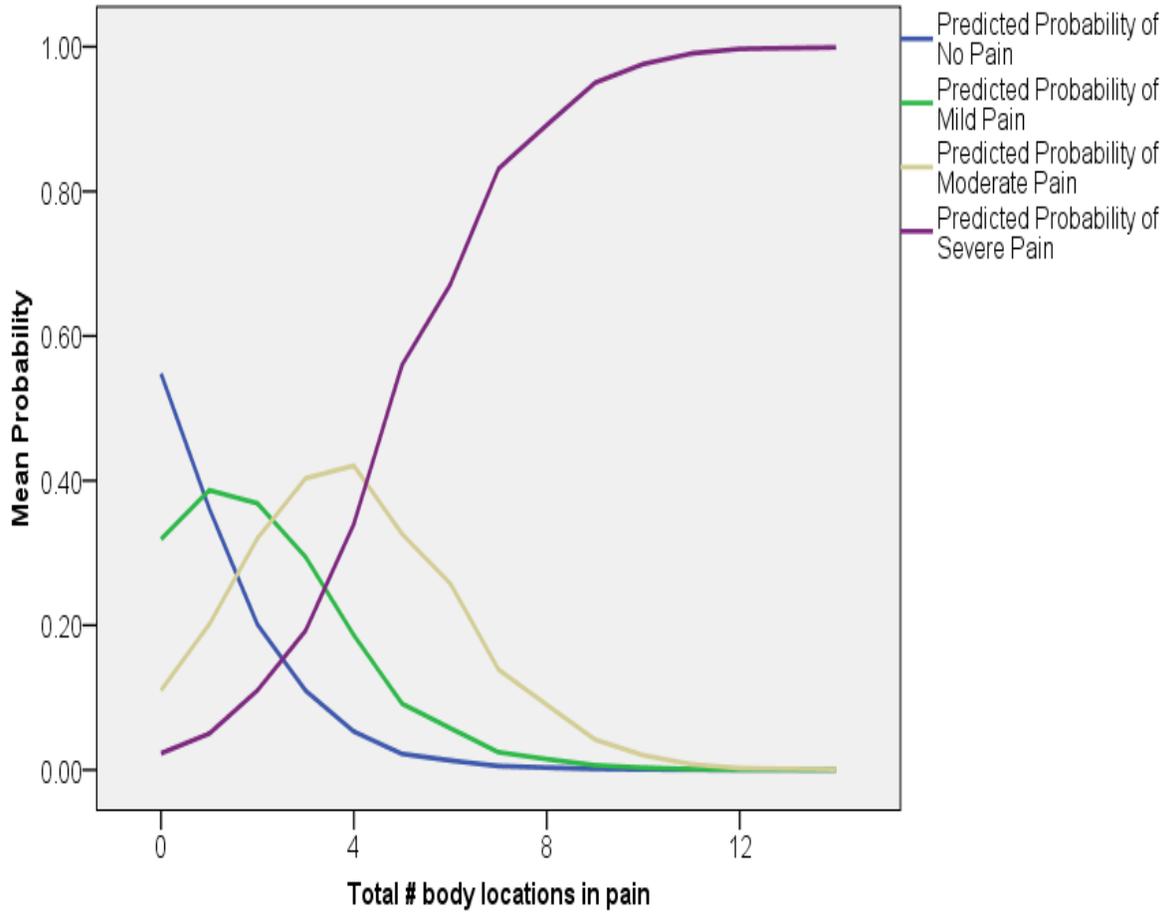
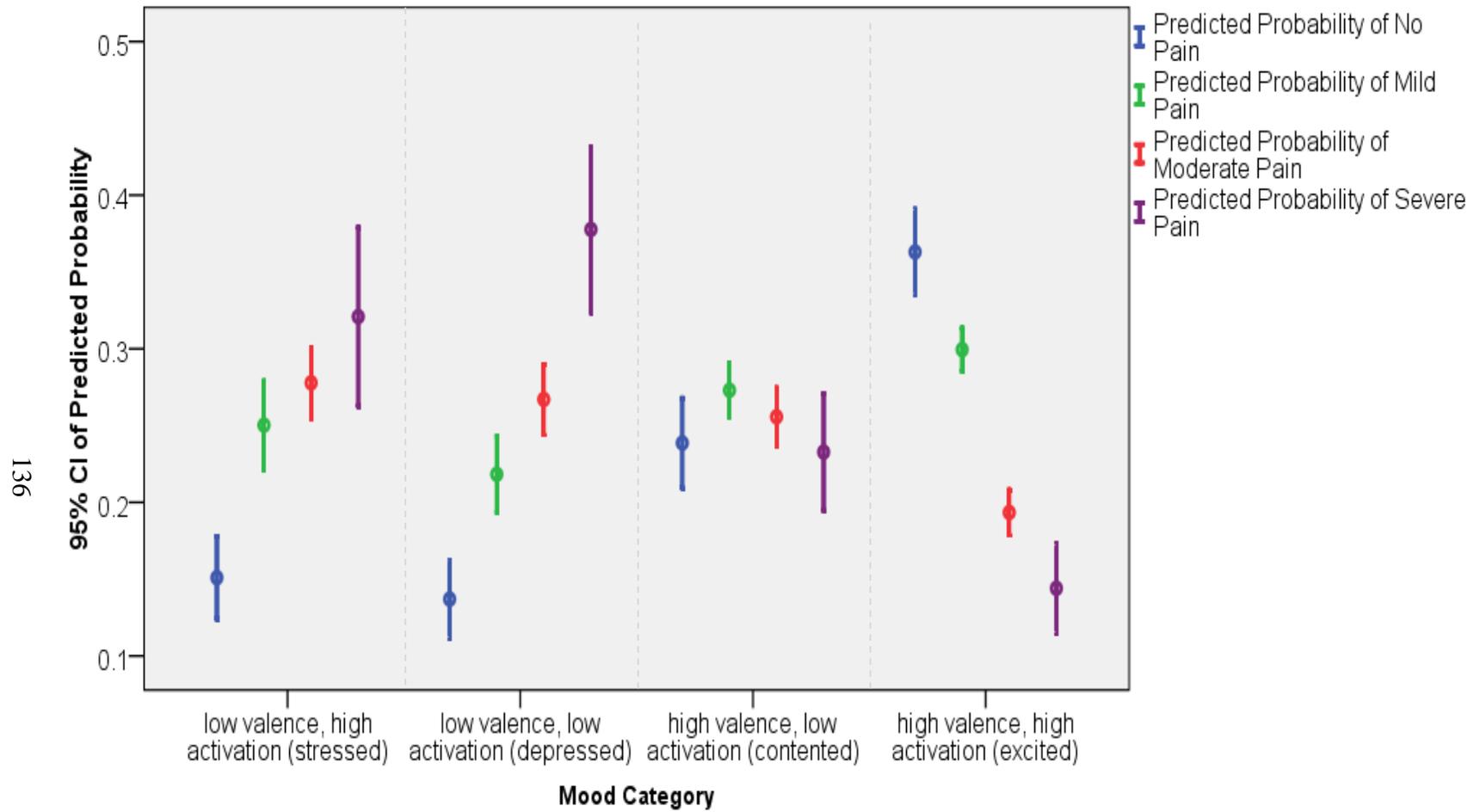


Figure 5-11: Predicted Probability of Pain Categories by Mood Categories



5.2.11.1.3 Activity and time of day

The results for the relationship between pain and activity will be presented for the combined dataset since the results for the combined dataset and the non-JIA group were the same. There was insufficient data in the JIA group dataset to test for an interaction between activity and TOD. A larger recruitment sample would be needed to examine this interaction in the JIA group. The main effects of TOD and activity on pain will not be interpreted separately for the combined dataset since there was a significant interaction between these variables. Pain intensity in youth with JIA and non-arthritic persistent pain conditions varies by time of day and by activity level. The effect of physical activity and inactivity on pain varies by time of day in the combined dataset. For interpretation, 95% confidence intervals for the predicted probabilities of occurrence of each of the four pain categories are compared in the following manner:

1. within activity level, between TOD (Figures 5-12a - 5-12d)
2. between activity level, within TOD (Figures 5-12e - 5-12h)

The direct relationship between activity and TOD was also examined using polytomous GEE in order to determine whether the effect of TOD on pain was mediated by a relationship between TOD and PA. The relationship between TOD and activity was borderline, but non-significant ($\beta=0.36$; 95% CI = -0.06, 0.78; $p=0.089$).

5.2.11.1.4 Within activity level, between TOD

Throughout the day, there is an increasing probability from morning to night of having no pain when sedentary with a statistically significant higher probability of no pain in the evening compared to the morning or during school ($\beta=1.67$; 95% CI = .67, 2.66; OR=5.3; $p=0.001$). Likewise, there is a trend towards reduced probabilities of moderate and severe pain throughout the day when sedentary .

There are no differences in the effect of time of day on probabilities of any of the pain categories when youth are lightly active.

There is a reduced probability throughout the day of having no pain when youth are more active, and an increased probability of having moderate or severe pain with activity from morning to evening. These relationships do not reach significance since the 95% CIs overlap across each time of day (Figure 5-12c, 5-12d).

5.2.11.1.5 Between activity level, within TOD

In the morning and during school hours, there is a significantly higher probability of having no pain when lightly active than when sedentary ($\beta=1.47$; 95% CI =.10, 2.84; OR=4.3; $p=0.036$). Likewise, during school, there is a significantly higher probability of having severe pain when sedentary compared to light activity.

After school, there is a non-significant trend for a higher probability of having no pain when sedentary or lightly active compared to high activity. In the evening, this relationship reaches significance in that there is a higher probability of having no pain when sedentary or lightly active compared to being highly active ($\beta=1.67$; 95% CI =.67, 2.66; OR=5.3; $p=0.001$).

In the evening, there is a significantly higher probability of having moderate pain ($\beta=0.92$; 95% CI =.01, 1.8; OR=2.5; $p=0.049$), and a non-significant trend to having severe pain when highly active compared to being sedentary or lightly active.

Figure 5-12: Predicted Probabilities of Pain Categories by Time of Day and Activity

Figure 5-12a: Probability of No Pain by Activity Level

Figure 5-12b: Probability of Mild Pain by Activity Level

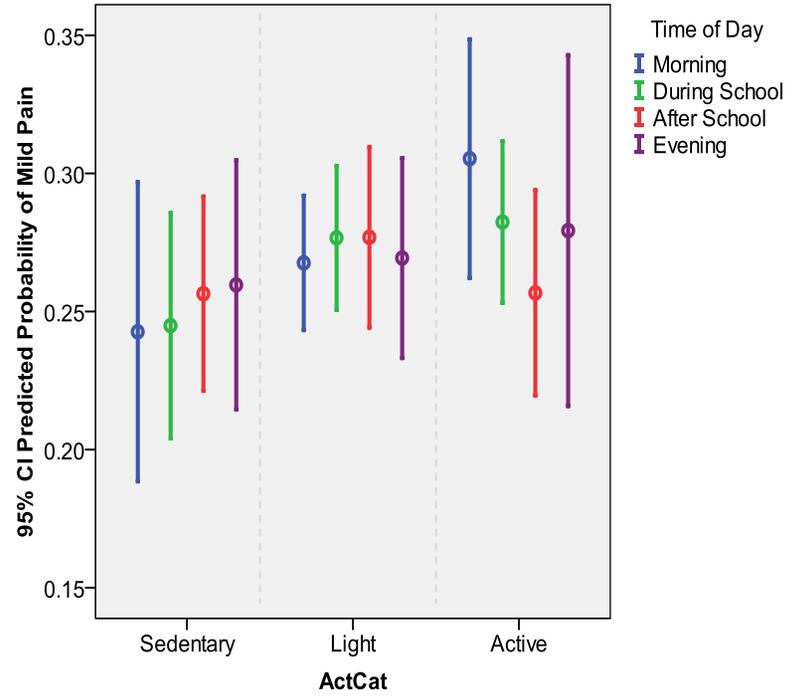
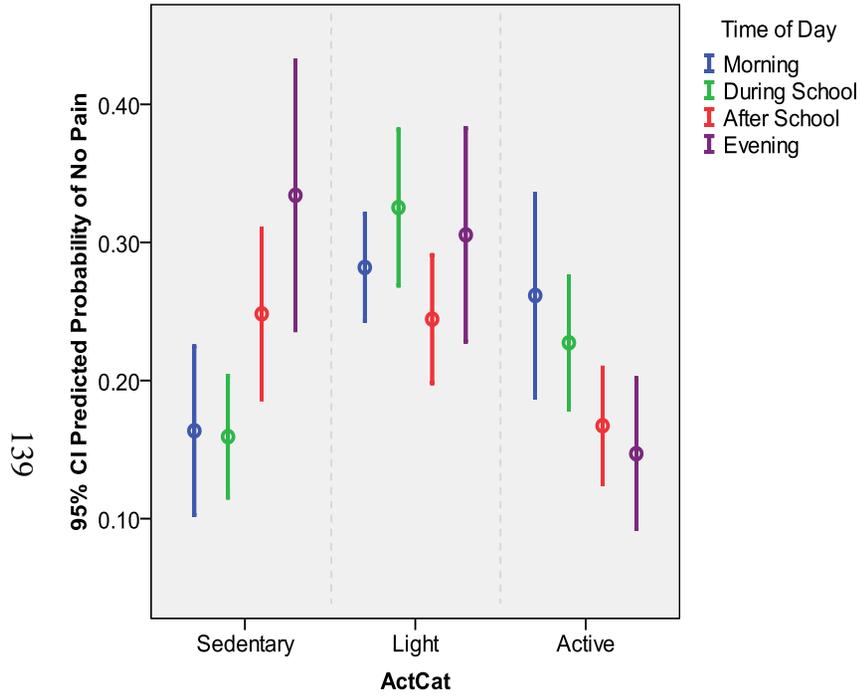


Figure 5-12c: Probability of Moderate Pain by Activity Level

Figure 5-12d: Probability of Severe Pain by Activity Level

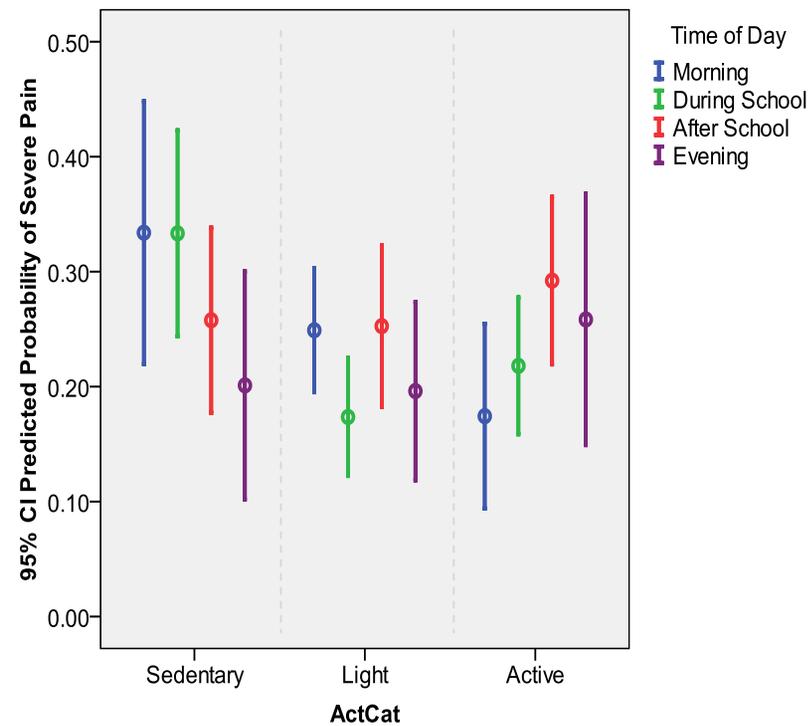
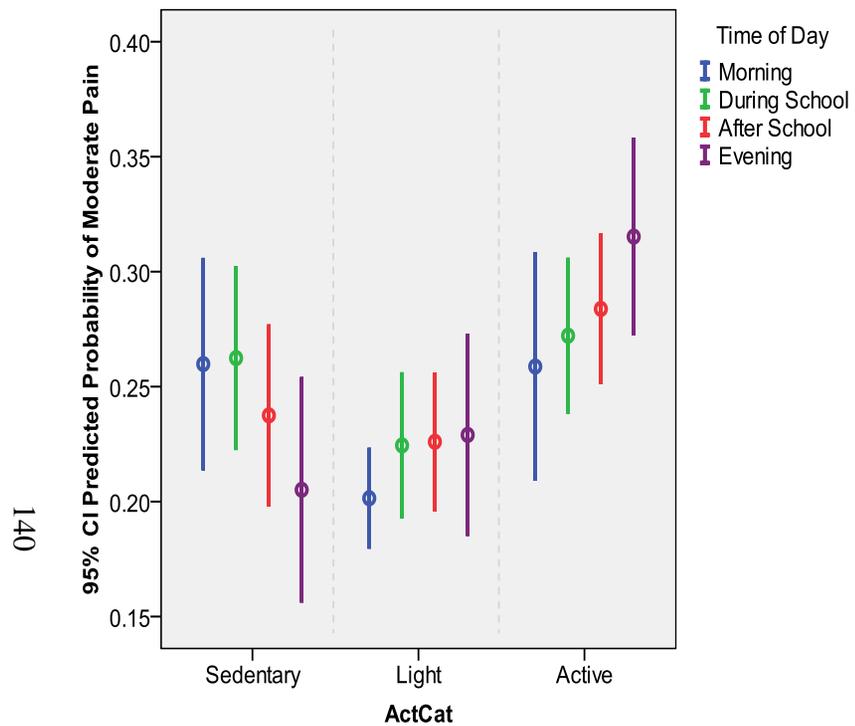


Figure 5-12e: Probability of No Pain by Time of Day

Figure 5-12f: Probability of Mild Pain by Time of Day

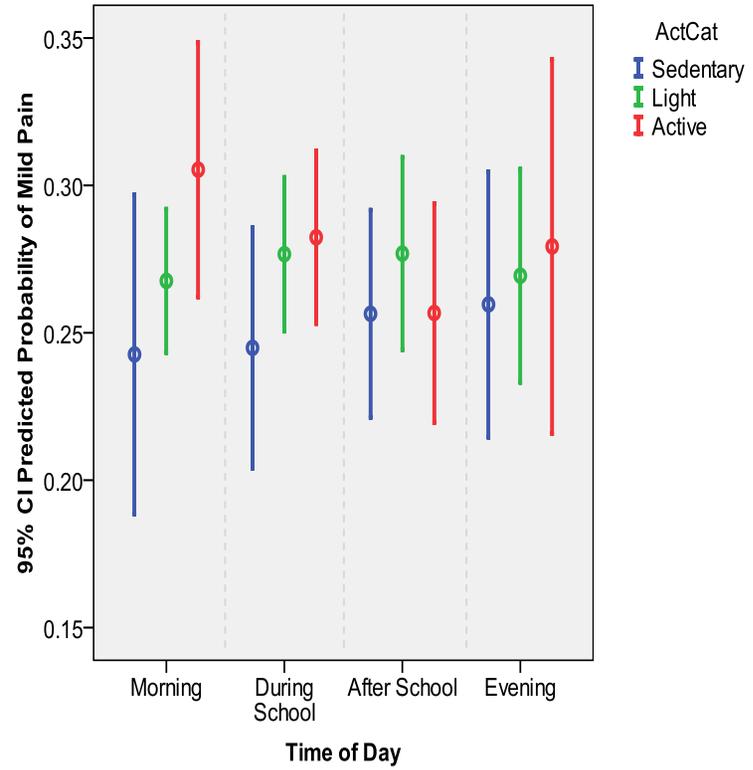
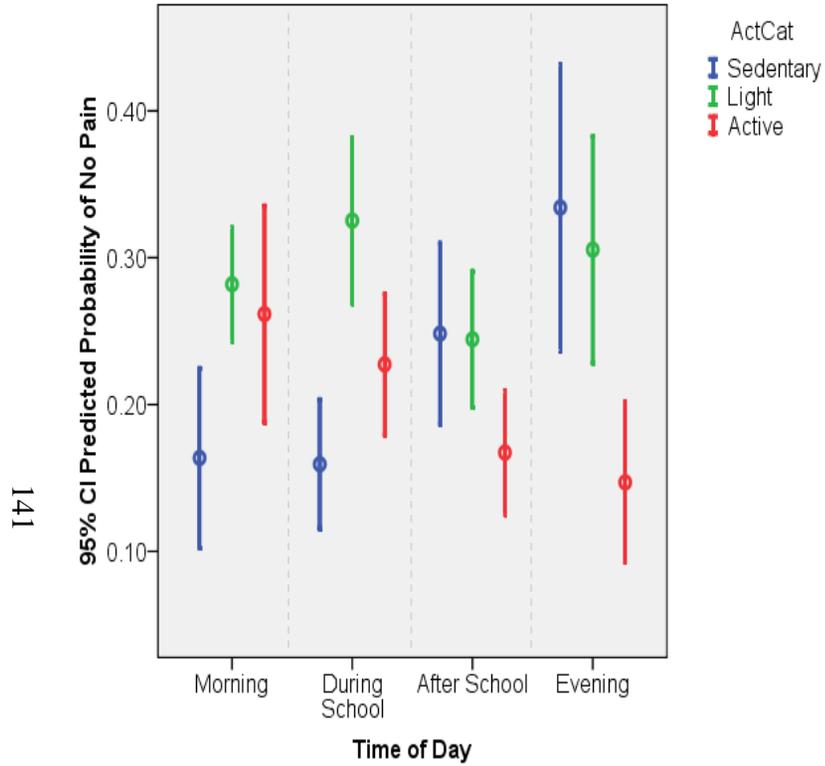


Figure 5-12g: Probability of Moderate Pain by Time of Day

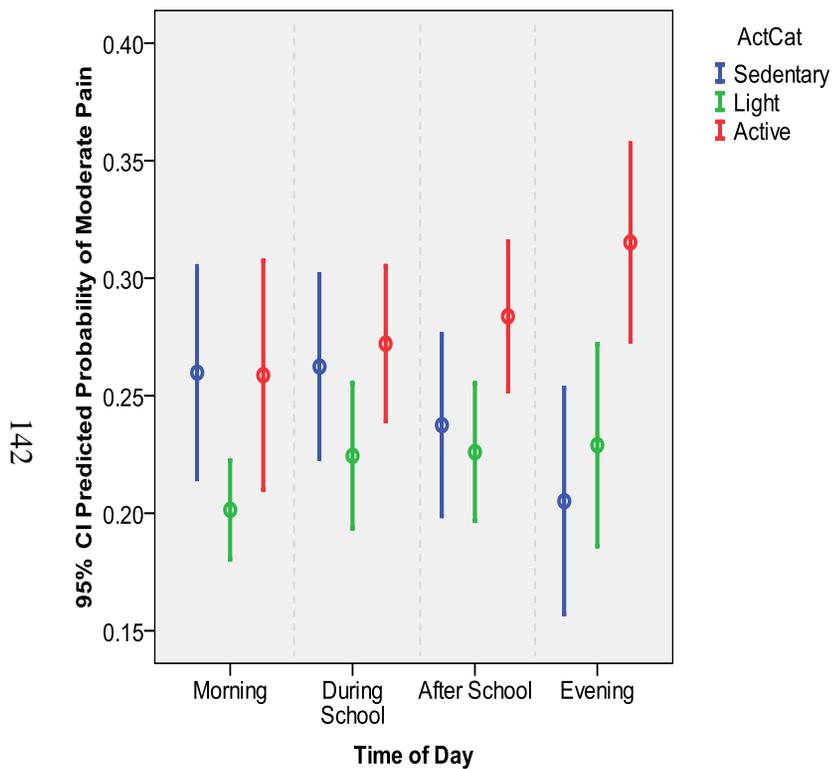
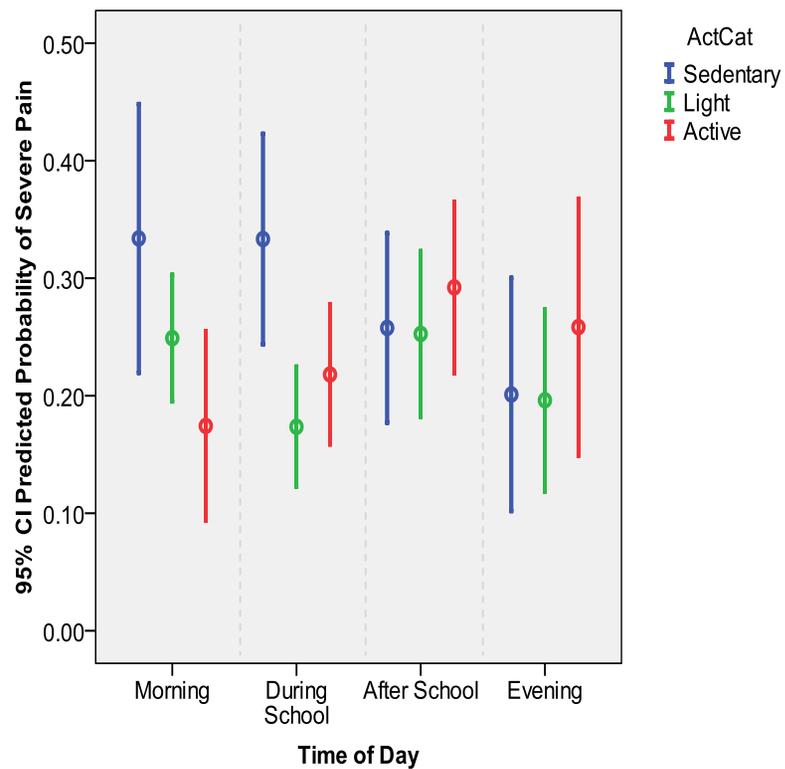


Figure 5-12h: Probability of Severe Pain by Time of Day



CHAPTER 6

6 DISCUSSION

The purpose of these studies was to examine the within-day temporal dynamics of pain in youth with JIA and a comparison group of non-arthritic persistent pain conditions. This chapter will begin with a discussion of the sample characteristics of both studies and the methods of analysis chosen. Within-day temporal dynamics of pain intensity, including systematic and irregular fluctuations in pain will be discussed based on the findings from both studies in relation to the research questions provided in Chapter 1 and the literature reviewed in Chapter 2. The implications of the research will be discussed with relevance to theoretical foundations as described in Chapter 3. The Vulnerability-Perturbation model of pain in children will be presented. The chapter will conclude with a summary of the study strengths and limitations, as well as implications for clinical practice and future research.

6.1 Sample Characteristics and Pain Characteristics

The demographic and disease characteristics of cases included in analysis in Study 1 did not differ significantly from those excluded. These characteristics are similar to those reported in other studies involving youth with JIA. ^(12, 16, 54, 99, 112, 202, 204, 214, 321-323) There were more male participants in Study 2 than Study 1 with just over half of participants in Study 2 being male. This is unusual considering the higher prevalence of arthritis and other pain conditions among females compared to males. None of the Study 2 participants had a diagnosis of systemic onset or oligoarticular onset JIA, yet these two subtypes accounted for over a third of the sample in Study 1. This affects the ability to generalize the Study 2 findings to the typical pediatric rheumatology JIA case load.

Of the 45 participants eligible for recruitment in Study 2, 32 enrolled, representing a participation rate of 71%. Thirteen youth refused participation in the study, citing busyness as the reason for refusal. The primary reason for ineligibility for recruitment was because youth did not

have arthritis or a pain condition, or they lived outside of the geographical boundaries of the study. A two hour driving radius geographical boundary was considered necessary for this study because of the high frequency of sampling. If there was an equipment loss or malfunction, the unit could be quickly replaced and the participant would be able to continue data collection with minimal interruption. However, by imposing this limitation, the enrolled participants were primarily urban living. This criterion also contributed to the limited ethnic and racial diversity of the sample since youth from remote northern First Nation communities were not eligible.

The original goal of recruitment for Study 2 was 15 youth with JIA and 15 youth with non-arthritic pain conditions. The recruitment period was extended by two months; however, one month of this was over the winter holiday season and school break which resulted in higher numbers of refusals to enrol. In the final month of recruitment, the decision was made to recruit a larger number of non-arthritis youth to compensate for the low numbers in the JIA group. The final recruitment included 13 youth with JIA, of which 11 were included in analysis and 19 youth in the non-JIA group, of which 17 were included in analysis.

The factor 'group' was included in the GEE analysis of the combined dataset, but found to not be a significant predictor of pain intensity. In addition, separate JIA and non-JIA group GEE analyses resulted in selection of the same main effects models. The final GEE models differed only in the inclusion of an interaction term between the JIA and non-JIA groups since there was insufficient data to conduct this analysis with the JIA dataset. Because of these two findings, analyses were presented with only the combined dataset.

Analysis was limited to those reporting at least one occasion of pain over the observation period since cosinor analysis cannot be conducted on a time series of no pain. Five cases were eliminated from analysis in Study 1 (4%) and 2 cases from Study 2 (6%) due to the lack of reported pain since these series were not appropriate for the method of analysis. Given this limitation, the results of the study can only be generalized to youth with JIA or non-arthritic pain conditions who report pain on at least one occasion over a 4 to 7 day period.

The pain characteristics reported by participants in both Study 1 and Study 2 are similar to those reported by other studies on pain in youth with JIA and other persistent pain conditions. (16, 22, 50, 54, 55, 95, 99, 201, 229, 299, 323-325)

6.1.1 Summary

Study 1 participants are representative of a typical JIA case load in a pediatric rheumatology clinic. Study 2 participants had a higher proportion of males and no youth with systemic or oligoarticular JIA subtypes. The geographical limitation of Study 2 resulted in an ethnically and racially homogeneous group. The analysis of both studies was conducted on time-series in which pain was reported at least once over the observation period. These limitations affect the generalizability of the study findings which will be discussed in Study Limitations.

6.2 Methods of Analysis

The distribution of pain intensity in both Study 1 and Study 2 can be described as compound distributions in the Tweedie family of distributions. This limits the methods of analysis available. These distributions are resistant to transformations, and there are no non-parametric methods for analysis that would provide a description of the time-varying nature of pain. Cosinor analysis was selected as one method of analysis for several reasons. First, cosinor analysis was used by several authors investigating within-day variability of pain in adult rheumatologic conditions. ^(27, 30, 142, 144, 147, 169, 326) Cosinor analysis was primarily selected for the first stage of a two-stage analysis procedure since it provides highly descriptive parameter estimates of the mean level of pain (mesor), variability (amplitude) and timing of peak pain (acrophase).

A limitation of cosinor analysis is the inability to detect rhythmicity unless it fits a cosine pattern. Lack of a significant fit does not mean that the data lack rhythmicity, rather, that the cosine curve is not the appropriate shape to describe the variability. ⁽¹⁶⁷⁾ Redfern et al. describe three non-sinusoidal within-day patterns of pain found in biological variables: saw-tooth, square wave, and ramp function. ⁽¹⁶⁷⁾ Jamison et al. used linear, quadratic and cubic regression to identify five similar within-day patterns of pain intensity in addition to a sinusoidal pattern: positive linear, negative linear, U-shaped, inverted U-shape, and flat. ⁽²⁴⁾ The saw-tooth pattern described by Redfern et al. is similar to the positive or negative linear patterns described by Jamison et al. in that the value of the variable rises or falls steadily throughout the day and returns to the baseline level in the morning. The patterns described as square-wave and ramp function by Redfern et al. are similar to the U-shaped and inverted U-shaped patterns of Jamison et al. in which the value of the variable is similar in the morning and evening. Although Nelson

⁽¹⁾ describes cosinor analysis as being adequate to describe most single-peak 24-hour patterns of variability, significance of the zero-amplitude test does not necessarily indicate that the cosine pattern is the most appropriate to describe the variability. This is most noticeable on visual inspection of the time plots from Study 2. Figures 5-9a and 5-9b were both significant on the zero amplitude tests, yet both series show prominent deviations from the fitted cosine curve. It is possible that there are overlapping rhythms resulting in deviations from a single-peak 24 hour pattern; however, it was not within the scope of this study to conduct more complex harmonic analysis of rhythms.

A further limitation of cosinor analysis is the need for imputations for missing data points. The method of imputation chosen, individual TOD means, had less of a biasing influence on the pain score distribution than random imputations. In addition, restriction of analysis to only those cases with 6 or more full days of data (the least number of imputations) resulted in a higher proportion of significant zero amplitude tests. Therefore, the influence of missingness and imputations appeared to have had minimal effect on the analysis, and resulted in more conservative cosinor estimates.

GEEs were used to examine the relationship between pain and TOD, physical activity and mood. GEEs were selected because of the non-normal distribution of the pain intensity data. A benefit of GEE analysis is that it can handle missing data and no imputations were required for analysis. The primary limitation of GEE as a method of analysis is the inability to model individual differences in the relationships between variables. Although multilevel mixed effects modelling could be used for this purpose, to date this method is only appropriate for datasets with approximately normal distributions.

An added limitation of both cosinor analysis and GEEs is that they are not easily incorporated into clinical use for analysis of pain diaries. Savedra et al. presented a method for scoring within-day changes in pain using the sum of dots on a dot matrix in which pain score (0 to 10) was charted over the course of a day.⁽¹¹¹⁾ The authors concluded that quantification of the dot matrix was impractical and difficult to interpret. They found that among youth with a variety of chronic and acute pain conditions, pain changes could be classified into one of six formats: steady decrease (13%), steady increase (3%), ongoing sharp increases and decreases (23%), stair step increase and decrease (22%), steady increase and decrease (22%) and constant pain (13%)

with 4% being unclassifiable. This suggests that there are many different patterns of change in pain other than what can be adequately examined with cosinor analysis. The heterogeneity of pain patterns may also confound analysis of TOD effect on pain by GEE. If it is found that within-day variability in pain can be used to identify subgroups in clinical populations and guide treatment decision making, further research is needed to develop a method of analysis that is acceptable and useful for clinicians.

6.2.1 Summary

Cosinor analysis was used to examine the data for systematic variability in pain intensity. In Study 2, GEEs were used to examine the relationship between physical activity and mood on irregular fluctuations in pain intensity. Both methods of analysis have strengths and limitations. Further research is needed to validate a simple method of analysis that can be used by clinicians to examine daily pain diaries for systematic or irregular variability.

6.3 Within-day Systematic Variability

Fluctuation in pain characteristics over the course of the day is widely acknowledged by individuals with persistent or recurrent pain conditions and their clinicians; however, this variability has been largely ignored in pediatric research and theoretical conceptualizations of pain. The sensation of pain would generally be considered an abnormal event and not an endogenous physiological process that would have a set rhythm. However, nociception and pain are influenced by physiologic processes that do have rhythmicity and any systematic variability observed in pain intensity could be attributable to such changes. Pain sensitivity appears to follow a circadian rhythm.^(133-135, 327) Therefore, if the threshold for nociceptive firing is reduced due to central or peripheral nervous system sensitization, pain may be seen to follow a circadian rhythm.

In the current studies, within-day variability in pain has been conceptualized as systematic and irregular variability. Systematic variability in pain intensity was examined using cosinor analysis with confirmatory analysis by GEE.

Despite differences in demographic and disease characteristics between samples, sampling frequency and length of observation period, both studies exhibited similar proportions of significant zero amplitude tests on cosinor analysis (Objectives 1.1 and 2.1). In both studies

the proportion of significant zero amplitude tests found in the clinical datasets exceeded the range of proportions found by chance with Monte Carlo simulation. This indicates that approximately one quarter of youth with pain conditions display systematic variability in pain intensity that can be described with a cosine pattern.

In Study 1, diagnostic subtype and higher age were predictive of a significant zero amplitude test. As hypothesized (Hypothesis 1.2), youth with systemic onset subtypes were more likely to display systematic variability in pain intensity. Youth with systemic onset JIA have more extra-articular manifestations, tend to have higher levels of inflammation, more widespread disease and greater disability than other JIA subtypes.^(80, 328) Youth with systemic onset JIA also have a unique cytokine profile compared to other types of JIA.⁽³²⁹⁾ Therefore, it is possible that systematic variability in pain is indicative of underlying disease mechanisms such as diurnal rhythms in inflammatory proteins such as IL-6 and genetic influences on cytokine rhythms.

As hypothesized in Study 1 (Hypothesis 1.2), age was a predictor of a significant zero amplitude test with older children being more likely to display systematic variability in pain. In Study 2, age was borderline significant; however, the 95% CI was wide (β 95% CI= 0.9, 4.2) and given a larger sample size age may have reached significance. Contrary to Hypothesis 1.2, female sex, higher PGADS, and higher total number of active joints did not predict significant zero amplitude test. In Study 1, 22.4% and in Study 2, 25% of series were significant. These proportions were lower than those reported in adult studies using similar analytic methods. Bellamy et al. found that 90% of adults with knee OA had significant cosine rhythms in pain intensity in time series of 10 pain measurements daily for 7 days.⁽¹⁴⁴⁾ In a larger study, Levi et al. found that 40% of adults with hip or knee OA had significant cosine rhythms in a pharmaceutical intervention study in which pain was measured 7 times daily for one day.⁽¹⁴⁷⁾ In separate studies, seventy-one percent of adults with hand OA,⁽²⁷⁾ and 48% of adults with fibromyalgia⁽¹⁴²⁾ had significant cosine rhythms.

The lower proportion of significant zero amplitude tests found in the present studies may be a result of younger age of the participants. Younger children may have a higher susceptibility to perturbations in pain from environmental stimuli such as the social context, emotional states or the physical environment. McGrath and Hillier suggested this when they wrote, "...children's

pain seems more plastic than that of adults, so that environmental and psychologic factors may exert a more powerful influence on children's pain perceptions." (26)

Perturbations resulting from physical or emotional stressors may disrupt an underlying systematic variability in pain intensity and result in greater irregularity in pain variability. An alternate explanation is that pain "neurosignatures" that occur with chronic health conditions may become more entrenched or stable over time resulting in a higher proportion of adults with systematic variability. Older adolescents also represent a different population than younger participants. A higher proportion of older adolescents recruited for the study would have a persistent disease course compared to younger children resulting from attrition of older youth who have gone into remission from the patient population. (12) In addition, age of onset of different subtypes of arthritis occur at different ages, (80, 328) in which case younger children would tend to have different disease subtypes than older adolescents and therefore display different patterns of pain variability. Further research is needed to determine if the presence of systematic within-day variability in pain is predictive of a persistent disease course and resistance to remission.

As hypothesized (Hypothesis 2.2), CHAQ score was a significant predictor of zero amplitude test on logistic regression in Study 2. Although this indicates that youth with higher levels of disability were more likely to have systematic variability in pain, this statistical test was underpowered to detect a true difference and may have been a spurious finding. This is evident by the extremely wide confidence intervals that indicate imprecision of the parameter estimates. Despite this limitation, this finding may be useful for future research question development. Lower physical activity participation, regularity of treatment regimen or differing underlying disease processes resulting in greater disability may all contribute to the systematic variability in pain seen in youth with higher CHAQ scores.

A wide range of parameter estimates were produced from the cosinor analysis in both studies, indicating inter-individual differences even among those with systematic variability in pain intensity. These results are similar to the findings of Levi et al. and Bellamy et al. who reported individual variability in cosinor parameter estimates in more homogeneous samples of adults with fibromyalgia or OA. (30, 142, 147) In both studies the acrophase (timing of peak pain) occurred in the morning for approximately 57% of those with a significant zero amplitude test.

There were insufficient numbers of significant time-series to conduct further analysis on subgroups based on the cosinor parameter estimates.

GEEs were used for confirmatory analysis to determine if TOD was a significant predictor of pain intensity. The results of the GEE from Study 1 both confirmed and showed differences from the results of the cosinor analysis. As hypothesized, pain intensity varied as a factor of time of day (Hypotheses 1.3.1) and the pattern of variation differed by subgroup of disease and sex (Hypotheses 1.3.2). Similar to the findings of cosinor analysis, youth with all subtypes had a higher probability of having the highest level of pain in the morning. This time of day effect was most pronounced for youth with systemic onset arthritis who had higher probabilities of moderate and severe pain at all times of day than youth with other subtypes.

Although sex was not a significant predictor in the logistic regression of the cosinor analysis outcomes, it was identified as a predictor on GEE in Study 1. Males were more likely to have moderate or severe pain in the morning and no pain in the evening. Females had a higher probability of having no pain in the afternoon and moderate or severe pain in the morning and evening, revealing a U shaped curve in pain intensity. This finding is similar to that of Keefe et al. who found that pain increased across the day for women, but decreased for men in a study involving 100 adults with OA in which pain was measured twice daily for 30 days.⁽¹⁷⁶⁾ Sällfors et al. found that females with arthritis reported more days with worst pain in the morning compared to males, but did not compare pain across the rest of the day between the sexes to determine if females experienced an increase in pain in the evenings.⁽⁹¹⁾

A possible reason for the different influence of sex on results of cosinor analysis and GEE is that cosinor analysis only fits a cosine curve to the data and is unable to identify other patterns of rhythmicity that may be present in the data. The logistic regression examined predictors of the 19 significant zero amplitude tests out of the 85 time series, whereas the GEE analyzed pain scores at each time point for all 85 time series. Sex may influence the relationship between time of day and pain due to subtype differences in prevalence for males and females. For example, oligoarticular arthritis and polyarticular arthritis have a much higher prevalence among females whereas enthesitis-related arthritis has a higher prevalence among males.^(80, 328) These subtypes differ in TOD effects on pain which may contribute to the differences in time of day effects on pain between males and females.

Contrary to Hypothesis 2.3.3, the effect of time of day on pain intensity did not differ by group on GEE analysis in Study 2. However, the sample in Study 2 is very heterogeneous and there were insufficient numbers of different JIA subtypes or non-JIA diagnostic groups to conduct subtype specific analyses. A larger sample with more homogeneous subgroups may have revealed separate group TOD relationships with pain, as was seen in Study 1.

In Study 2, abnormal flattened cortisol profiles were detected in only three participants. Two were in the JIA group and one in the non-JIA group. All three participants had non-significant zero amplitude tests on cosinor analysis. Data were not collected on oral corticosteroid medication use. This may have confounded the ability to detect a naturally occurring altered diurnal pattern of cortisol production. However, the hypothesis was that a flattened cortisol profile would be related to a morning peak in pain, which if corrected by corticosteroid use, would no longer be an influential factor. It is possible that with a larger sample size greater heterogeneity may have been detected in diurnal cortisol patterns. The criteria of Smyth et al. used to assess daily cortisol patterns were based on 6 samples per day for 2 days,⁽³³⁾ whereas the current study used only two measures per day averaged over the four days. In the Smyth et al study, 51% of the community living adult participants showed a strong descending diurnal pattern from morning to evening.

In our study, approximately 30% of participants had an inconsistent pattern between day one and day two of the study and 17% showed a flattened cycle on both days. It is possible that inconsistency between days masked an altered diurnal cortisol pattern in some participants. Further investigation is needed to determine if alternative criteria are more sensitive for detecting altered diurnal cortisol patterns or other measures of altered cortisol production that may be a relevant influence on within-day pain variability. Knutsson et al. examined mean diurnal cortisol levels using area under the curve (AUC) analysis on cortisol from 7 serum samples taken over one day from 235 healthy youth.⁽³³⁰⁾ However, the AUC analysis would be unable to detect a diurnal profile of either a descending or flattened slope throughout the day. Harville et al. examined salivary cortisol collected from pregnant women 5 times per day for 3 days.⁽²⁶⁹⁾ They computed four measures of cortisol variability: mean AUC, mean daily maximum, mean amplitude (maximum-minimum) and the mean morning rise (difference between wake + 30 minutes and wake samples). There was a strong correlation between the mean AUC of 15

cortisol measures and a subset of data simulating a twice per day (morning and evening) measurement protocol ($r=0.775$, $p<0.01$).

Flattened morning cortisol levels have been implicated as a possible cause of higher morning pain in adults with rheumatoid arthritis. ^(28, 190) Picco et al. also found normal daily cortisol rhythms in youth in remission from oligoarticular JIA, but increased circulating levels of the hormone ACTH in the morning. ⁽¹⁹¹⁾ Since ACTH leads to increased production of cortisol, the authors concluded that higher levels of ACTH in the absence of higher levels of cortisol indicated an impaired cortisol production due to a partial resistance to ACTH and an impaired HPA axis function. Therefore, normal cortisol profiles in youth with active disease found in the current research do not necessarily preclude the presence of abnormal HPA axis function which could result in systematic variability in pain intensity.

Further research is needed to determine if indicators of abnormal HPA axis function, other than cortisol profile, are able to explain inter-individual differences in systematic variability of pain intensity. For example, the ACTH/cortisol ratio may be a more sensitive indicator of altered HPA axis function in youth with JIA. ⁽¹⁹¹⁾ The cortisol arousal reaction (CAR) is the spike in cortisol production that occurs within the first 30 to 60 minutes after waking in healthy adults and is an indicator of adrenal gland function. ⁽³³¹⁾ Several stressor paradigms have been utilized in research with children and adolescents for examining the responsiveness of the HPA axis to stressful situations. ^(332, 333)

6.3.1 Summary

Approximately one in four youth with pain from arthritis or non-arthritic pain conditions display systematic variability in pain intensity that can be described with cosinor analysis. Older youth, and youth with systemic onset JIA are more likely to exhibit this pattern of systematic variability. Within-day patterns of pain other than a cosine pattern are identifiable as time of day is a significant predictor of pain on GEE. Males and females display different within-day patterns of pain, and within-day variability differs by subtype of arthritis. Youth exhibiting systematic variability in pain intensity may signify a subset of the population that is either less susceptible to perturbations in pain from environmental stimuli or those with altered central or peripheral sensitivity which lowers the threshold for nociception allowing circadian rhythms in pain sensitivity to manifest as systematic variability in pain. Further research is needed to

determine if abnormal HPA axis function or altered cytokine profiles explain the systematic variability seen in this subset of the population. Further research is also needed to determine if systematic variability in pain is predictive of persistent disease or other disease outcomes that lead to higher levels of disability, such as joint erosions, contractures or motor impairments.

6.4 Within-day Irregular Fluctuations

Factors that increase (trigger or aggravate) or decrease (alleviate or eliminate) pain contribute to irregular fluctuations in intensity. Movement of inflamed joints, loading of joints with cartilaginous erosions or contractures, or mechanical stresses on muscles that are atrophied due to disuse or pathological changes may contribute to pain triggers or irregular fluctuations in pain with movement. ⁽³⁹⁾ Effective treatment with pharmaceutical or non-pharmaceutical interventions may reduce or eliminate pain. Positive mood has been associated with lower daily pain in youth with JIA and changes in mood states during the day may contribute to irregular fluctuations in intensity. ⁽⁵⁰⁾ The focus of the GEE analysis of Study 2 was on the short-term relationship between pain and physical activity and pain and mood. Several other variables could have been investigated for contributions to within-day pain variability, such as medication use, non-pharmacological interventions, physical and social environments, diet, and sleep quality. While these were not examined in order to narrow the scope of this study, this is an important direction for future investigations on within-day pain variability.

6.4.1 Physical Activity

In Study 2, changes in physical activity were examined for their relationship with pain intensity in youth with JIA and non-arthritic pain conditions. The majority of studies examining the relationship between activity and pain have utilized cross-sectional survey designs which preclude the ability to detect a temporal direction in the relationship. The current research used a study design in which pain was assessed at the end of two hour windows of physical activity. This design allows for an examination of the temporal relationship between activity and pain which is necessary if a causal relationship is to be established. ^(159, 334) The design only allows for identification of a short-term relationship between physical activity and pain. Delayed responses of changes in pain, such as with delayed onset muscle soreness would not be identifiable with this study design.

In Study 2, physical activity was operationalized as a categorical variable with 3 nominal levels; sedentary, light, and active. Categories were based on quartiles of accumulated MVPA and sedentary minutes from the total sample. Construct validity of the categorization of activity was based on the moderate relationship found between mean activity categories and PAQ score. Physical activity and inactivity were combined into a single activity construct because it was hypothesized (Hypothesis 2.3.2) that there would be a parabolic relationship between pain and activity and inactivity in which both high moderate to vigorous activity and high sedentariness would contribute to increased pain.

A complex relationship was identified between activity level and pain that varied by time of day. In the morning and during school hours, light activity is associated with lower levels of pain and sedentariness is associated with a higher probability of severe pain.⁶ The trend is partially reversed in the after school and evening hours in that higher levels of activity are associated with higher probability of moderate to severe pain and light level active or sedentariness is associated with a higher probability of no pain. Overall, there was a non-significant trend towards a U shaped relationship between pain, activity and sedentariness in support of hypothesis 2.3.2. Both sedentariness and physical activity are associated with a higher probability of moderate to severe pain at different times of day; however, light activity is associated with in a higher probability of no pain at all times of day. Although causality cannot be determined by this study alone, the design of this study allows for the identification of a short-term temporal association between different activity levels and pain intensity. There is a higher probability that light level of activity will immediately precede a lower pain intensity score. Contrary to the hypothesis (Hypothesis 2.3.4) the relationship between physical activity and pain intensity did not differ by group or by sex; however, the sample was predominantly non-JIA, and combined analyses may have masked subgroup specific JIA patterns with pain. In addition, the sample was very heterogeneous and included 5 of the 7 JIA subtypes and 6 different sub-classifications of non-JIA pain conditions. Larger, more homogeneous samples may have

⁶ There were only three occasions in which youth were highly active between 6:00 and 8:00 am; therefore, the strength of this trend comes primarily from the 8:00 to 10:00 activity window.

revealed more distinct relationships between physical activity and pain. However, general trends have been identified which can be used to support future research question development.

The findings of Study 2 support treatment recommendations which encourage light physical activity for youth with JIA and other persistent pain conditions. Light movement in the early part of the day may ease discomfort from morning stiffness and the gelling effect which contribute to increased pain intensity.

Accumulation of long periods of sedentariness, particularly in the morning and during school, is associated with an increased probability of pain. This finding is supported by other studies that found a relationship between prolonged computer use and pain. ^(44, 45, 231)

Categorization of sedentary activity in Study 2 required youth to accumulate no more than 11 minutes of MVPA, but more than 90 minutes of sedentary time in a two hour window. The findings of this study support the recommendation that youth with pain conditions may benefit from interruption of sedentary activities in order to accumulate more than 30 minutes of light activity every two hours. Youth, their parents or health care providers should discuss with teachers and employers the benefit of frequent activity breaks for youth with pain conditions to avoid sustained positions in school or work. Youth may benefit from interruptions in sedentary activities in the mornings outside of school hours.

After school and in the evening, higher levels of activity are associated with a higher probability of moderate to severe pain. A possible reason for this could be an interaction between fatigue, activity, and pain. Although fatigue was not measured in Study 2, previous studies have found that pain intensity is related to fatigue which interferes with physical activity participation. ^(36, 37, 321, 335) If fatigue increased over the course of the day, as is typically reported, youth may find that participation in MVPA during times of higher fatigue results in higher pain. Another explanation may be that there is a summative effect throughout the day in which accumulated physical activity has a greater impact as the day progresses. A combined experimental and observational study design would be necessary to investigate this hypothesis. For example, a randomized controlled trial could be conducted in which youth with JIA could be randomized to either a fatiguing physical activity protocol or control group protocol. Within-day pain variability could be monitored in participants for several days prior to and following the fatiguing activity to

examine if the relationship between physical activity and pain remains consistent following the fatiguing activity.

A third possible explanation is that physical activity in the evening exerts a different influence on the HPA axis than in the morning, resulting in a unique physiological response to exercise at different times of day. In the morning, healthy individuals display a circadian peak in IL-6 and a resulting up-regulation in cortisol production. In effect, the HPA axis and immune response is primed towards defense and resolution of inflammation in the morning. Physical activity at this time of day may result in a less intensive immune response than in the evening, thereby resulting in a muted pain response to exercise in the morning. Further research is needed to examine the immune response to physical activity in youth with pain conditions and possible time of day interactions. In particular, it would be important to examine the timing of production of pro-inflammatory cytokines such as interleukin-6, which are known nociceptive biochemicals⁽³³⁶⁾ produced by contracting skeletal muscle in proportion to the intensity and duration of exercise⁽⁴³⁾ and to determine if there are circadian variations in immune response to physical activity.

Categorization into the highest level of activity required youth to accumulate at least 11 minutes of MVPA and to accumulate no more than 90 sedentary minutes in a two hour window. Youth are encouraged to participate in regular physical activity with the goal of meeting internationally accepted physical activity guidelines of 60 minutes of MVPA daily.⁽³³⁷⁾ Pain is an added barrier to physical activity participation that must be managed if youth are to meet these guidelines. Youth with pain conditions may benefit from shorter bouts of physical activity throughout the day, rather than a single longer bout of exercise. Youth with pain conditions should discuss with their health provider if prophylactic treatments to reduce pain during physical activity are appropriate. Further research is needed to determine if the timing of physical activity participation and the activity dose (duration, frequency and intensity) can be modified to make physical activity less painful for youth with pain conditions.

The activity categories were based on group quartiles of minutes of MVPA and sedentary minutes. Participants in Study 2 exhibited a wide range of general physical activity participation (PAQ range = 1.3 to 3.9) suggesting an equally wide range of fitness levels. Individualized cut points for activity classification may have yielded a clearer relationship between activity and

pain. A further limitation of this study is that we did not screen for neuropathic pain symptoms which would have enabled distinguishing between participants with neuropathic, nociceptive or combined (coinciding nociceptive and neuropathic) pain conditions.

6.4.2 Mood

As hypothesized (Hypothesis 2.3.1), the results of Study 2 demonstrate a strong within-day relationship between pain and mood for youth with JIA and other pain conditions. Within-day fluctuations in mood are associated with, and may contribute to within-day variability in pain. In this study, co-occurring reports of mood and pain were measured; therefore a temporal relationship and a direction of causality cannot be determined using this study design. Although changes in mood may contribute to changes in pain, the reverse direction of influence may also result in the relationship seen in this study. Changes in pain may be the cause of changes in mood. A study by Feldman et al. found a bidirectional relationship between pain in a daily diary study on adults with chronic pain in which lagged analysis showed that higher pain resulted in next day negative (angry) mood and depressed mood resulted in next day increased pain. ⁽³³⁸⁾

Results of the current research showed that overall there was a higher probability of severe pain and a lower probability of no pain during times of low mood. This relationship was significant at both low valence-low activation and low valence-high activation mood categories; however, the relationship was more distinct in the low valence-low activation category. Positive mood (high valence, high activation) was associated with a significantly higher probability of no pain and lower probability of severe pain. No relationship was seen between pain and mood at times of high valence-low activation. Low activation-low valence may be considered the lowest mood category within this model with a distinct separation between pain categories and higher probability of severe pain. Likewise, high valence-high activation may be considered the highest mood category with higher probability of no pain.

Previous studies have reported that day to day changes in recalled reports of mood are related to daily recalled scores of pain intensity. ^(16, 50, 176, 338) Studies by Schanberg et al. operationalized mood as a uni-dimensional construct using the Facial Affective Scale to measure mood, ^(16, 50) whereas Keefe et al. used the Profile of Mood States questionnaire which is an 18 item composite index of positive and negative affective states. ⁽¹⁷⁶⁾ In the current research, a two dimensional construct of mood that incorporates emotional valence and emotional activation

identified a relationship between mood and pain intensity in the expected direction. This supports the use of a two-dimensional model of mood in studies of momentary pain in youth which is more informative than the uni-dimensional construct yet more parsimonious, less time consuming to administer, and less complex to analyze and interpret than the 18 item index.

Group differences were identified in the frequencies of mood categories. Youth in the JIA-group generally reported higher emotional activation and more positive mood. It is also possible that there are interindividual differences in the relationship between pain and mood; however, this analysis was not within the scope of this study.

6.4.3 Summary

The findings of Study 2 further clarify the complex relationship between activity, inactivity and pain by the identification of an interaction with TOD. Light activity was associated with a higher probability of no pain and a lower probability of moderate or severe pain at all times of day. Although this relationship was not consistently statistically significant, this finding generally supports the concept of a U shaped relationship between physical activity and pain, in which light activity is associated with a higher probability of no pain compared to high activity and sedentariness. Sedentariness, particularly in the morning, is associated with a higher risk of pain, whereas higher levels of physical activity are associated with increased probability of higher pain in the evening. This study allowed for the examination of the temporal direction of the relationship between pain and activity in support of a causal relationship in which physical activity and inactivity contribute to the irregular within-day variability in pain intensity. Further research utilizing experimental designs are needed to confirm the causal nature of this relationship.

Youth may benefit from participation in regular light physical activity and avoidance of accumulation of sedentary minutes in the morning and during school. All youth, regardless of type of pain condition, should work with health care providers to develop a physical activity plan which may include shorter bouts of MVPA throughout the day. Further research is needed to examine the relationship between physical activity, fatigue, pain and time of day, the immune response to physical activity in youth with pain conditions, appropriate dosing and timing of activity interventions, and the effect of pain preventative interventions during physical activity.

These findings also further our understanding of the relationship between pain and mood in that there is a momentary relationship between mood and pain reported throughout the day. Although further research is needed to establish a temporal direction and causal relationship between pain and mood in youth, within-day changes in mood may contribute to irregular within-day variability in pain. Use of a two dimensional construct for mood is effective in demonstrating the expected relationship between pain and mood.

6.5 Theoretical Considerations

The current research contributes to the description and understanding of within-day variability in pain intensity experienced by youth with JIA and non-arthritic pain conditions. Both systematic and irregular within-day variability have been defined and described in this population and factors affecting variability have been identified. This research provides a foundation for future studies on within-day variability of pain. Further research is needed to determine if within-day variability, either systematic or irregular, is predictive of disease course and outcome, and if patterns of pain can be used to differentiate underlying disease processes and provide guidance for treatment decision making. Previous research has shown that pain variability influences treatment response in adults with fibromyalgia in that those with larger pain fluctuations show a greater treatment response. ⁽³³⁹⁾

Irregular within-day fluctuations in pain may represent a vulnerability to perturbations on an underlying systematic pattern of pain sensitivity. In the current research, pain varied by time of day for youth with JIA and the pattern of variability differed by diagnostic subtype, age and sex. A subset of youth with pain exhibit a stable within-day cosine rhythm to pain. The findings of these studies suggest that other patterns may be identifiable with further analysis. The current research also found that irregular within-day variability in pain is influenced by physical activity and inactivity, with contrary effects at different times of day. Irregular fluctuations in pain intensity were also associated with changes in mood. Interindividual differences in the relationship between pain and mood or physical activity have been identified in adult pain populations which supports the conceptualization of different subgroups of variability. ^(38, 176, 228, 338) Future research investigating pain variability must be guided by a theoretical framework which can be used to conceptualize the temporal dynamics of pain.

6.5.1 Deficits of Existing Models

Although the biobehavioral framework of McGrath and Hillier identifies specific time-varying factors on pain perception in children, it lacks integration of time-varying biological factors of influence. ⁽²⁶⁾ The neuromatrix theory identifies numerous broad categories of influence that are regulated by the neuromatrix and may contribute to pain neurosignature outputs including both tonic (stable) and phasic (time-varying or situational) inputs from the brain and periphery. ⁽²⁵³⁾ However, neither of these models account for potential structure or characteristics of pain variability that would be distinguished as either systematic variability or irregular fluctuations. In addition, neither the McGrath and Hillier model, nor the neuromatrix model provide a framework for identifying differences between individuals in susceptibility to perturbations in pain by situational factors.

The Vulnerability Diathesis Stress (VDS) model of Dworkin et al., ⁽⁵⁾ outlined in chapter 3, provides a testable framework for examining the causal pathway for the pathogenesis of persistent pain rather than simply identifying possible stable or situational factors of influence. However, the VDS model was developed as a framework for understanding the development of a persistent pain condition rather than examining the temporal dynamics of pain which may be more relevant from a therapeutic perspective.

A testable model is needed for children's pain that builds upon the foundational premise of the GC theory, biobehavioral theories and neuromatrix theory that view pain as a complex, dynamic process resulting from the integration and regulation of numerous peripheral and central nervous system processes. The model should provide a construct for the differentiation between systematic and irregular variability. The model should also provide a framework to examine between-person differences in vulnerability to perturbations in pain that would contribute to the development of novel therapeutic approaches if risk factors are found to predict vulnerability to perturbations and if vulnerability to perturbations is found to be modifiable. This model will also assist clinicians in explaining to patients why pain changes throughout the day and across days despite the stability of the diathesis. The Vulnerability Perturbation model presented in this chapter extends the model of Dworkin et al. to provide a testable model for hypothesis building for examination of individual differences in pain variability and vulnerability to perturbations in pain.

6.5.2 Vulnerability Perturbation Model of Pain

6.5.2.1 Vulnerability

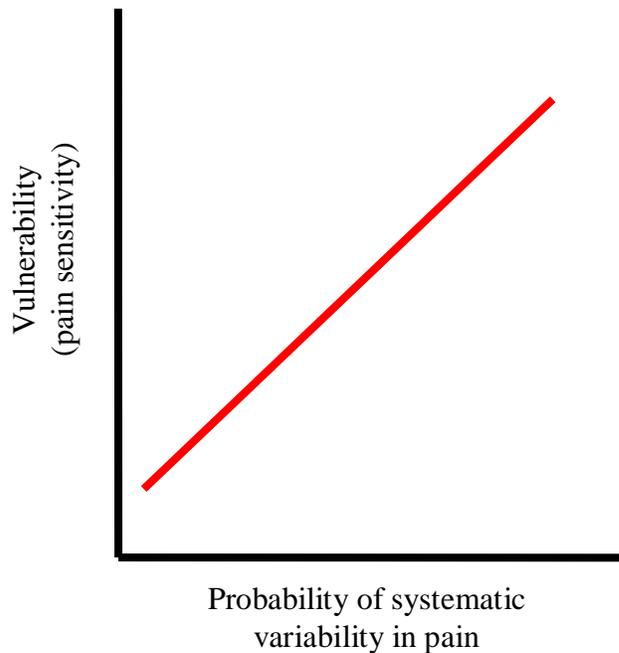
In the VDS model, Dworkin et al. described vulnerability as the risk of development of chronic pain with contributions from diverse predisposing biological, psychological and social factors. ⁽⁵⁾ The VDS model proposes that chronic pain conditions arise from the interaction between the level of vulnerability (biopsychosocial predisposing factors) with the diathesis (injury or illness) and stressors (recent stressful life events, lack of social support), each exerting a continuum of influence.

In the Vulnerability Perturbation model (VP), the interacting influences of the vulnerability, diathesis and stress are reduced to form a single construct of vulnerability. The social determinants of health bring together the vulnerability, diathesis, and stress continuums of the VDS model. Therefore the vulnerability factors in the VP model are expanded to include all of the social determinants of health identified by Health Canada, including: income and social status, employment, education, social environments, physical environments, healthy child development, personal health practices and coping skills, health services, social support networks, biology and genetic endowment, gender and culture. ⁽³⁴⁰⁾

Negative facets of these determinants (e.g. low income, unhealthy social and physical environments or genetic vulnerabilities) may work together to act on a continuum of influence on the HPA axis immune responsiveness and central and peripheral nociceptive environments to reduce thresholds for nociception. At higher levels of vulnerability, individuals will have greater sensitivity to pain and be more prone to development of persistent pain conditions. This is supported by previous research on pain sensitivity and the epidemiology of pain which has identified the following risk factors: female sex, older age, socioeconomic status, culture, lifestyle factors, employment status and occupational factors. ⁽³⁴¹⁻³⁴⁵⁾ In the absence of perturbations, greater pain sensitivity will manifest as systematic variability in pain intensity for those with a diathesis resulting in a persistent pain condition (Figure 6-1). This is supported by the findings of Bellamy et al. who reported that women with greater pain sensitivity were more likely to display a significant cosine rhythm to pain intensity. ⁽¹⁴²⁾ It is hypothesized that the pattern of systematic variability will be related to genetically programmed circadian timing of pain sensitivity as well as underlying disease processes. This is supported by research on the

circadian variability of experimental pain sensitivity and clinical pain in adults reviewed in Chapter 2, Section 3.

Figure 6-1: Relationship between vulnerability and systematic variability



6.5.2.2 Perturbation

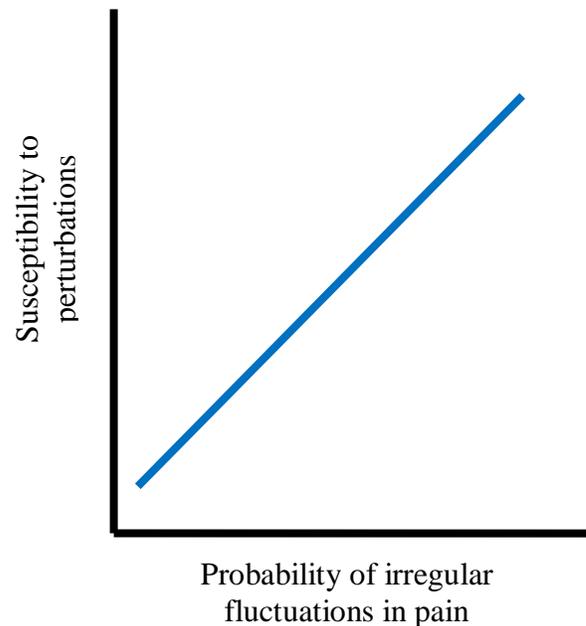
In the VP model, it is proposed that there are inter-individual differences in susceptibility to perturbations in pain. This susceptibility may be related to demographic characteristics. For example, in Study 1, with increased age participants were significantly more likely to display systematic variability in pain, and age was borderline significant as a predictor of systematic variability in the logistic regression of cosinor outcomes in Study 2. Therefore, younger children may be more susceptible to perturbations in pain. Susceptibility may be related to biological and psychological characteristics. For example, significant between-person variability in HPA axis reactivity to stressors has been identified and linked to genetic variants and environmental exposures.⁽³⁴⁶⁾ Both hypo-reactivity and hyper-reactivity of the HPA axis in response to stress have been associated with several diseases such as depression, Alzheimer's, fibromyalgia and rheumatoid arthritis.⁽³⁴⁶⁻³⁴⁸⁾ Fibromyalgia and rheumatoid arthritis are both associated with a

blunted response of the HPA axis to physical or psychological stressors, ⁽³⁴⁷⁾ and the majority of adults with these conditions display systematic variability in pain intensity. ^(30, 142) It is proposed that a hyper-reactive HPA axis response to stress is associated with higher susceptibility to perturbations in pain and a higher probability of irregular variability in pain intensity. Likewise, a blunted HPA axis response to stress is hypothesized to be associated with lower susceptibility to perturbations in pain and a higher probability of systematic variability in pain.

Further research is needed to identify factors that contribute to susceptibility to perturbations and determine if it is a stable characteristic over time, or whether it can be manipulated with interventions. Identification of altered HPA axis reactivity may be useful in distinguishing individuals with greater susceptibility to perturbations in pain. ⁽³⁴⁹⁻³⁵¹⁾

It is proposed that susceptibility to perturbations exerts a continuum by which individuals who are more susceptible display greater within-day irregular fluctuations (Figure 6-2) in pain and stronger associations between pain and time varying factors such as physical activity and mood. However, it is proposed that individuals with greater susceptibility to perturbations will also show greater response to interventions and changes in the environment. For example, these individuals may be found to experience a more noticeable and immediate relief in pain from pharmaceutical and non-pharmaceutical therapies. This interaction between vulnerability and perturbation may explain why Harris et al. found substantial inter-individual differences in pain variability in adults with fibromyalgia and that those with greater pain variability were more likely to be classified as responders in a drug trial. ⁽³³⁹⁾ It is interesting to note that those with greater variability showed a stronger response to both the therapy and the placebo.

Figure 6-2: Relationship between susceptibility to perturbations and irregular fluctuations



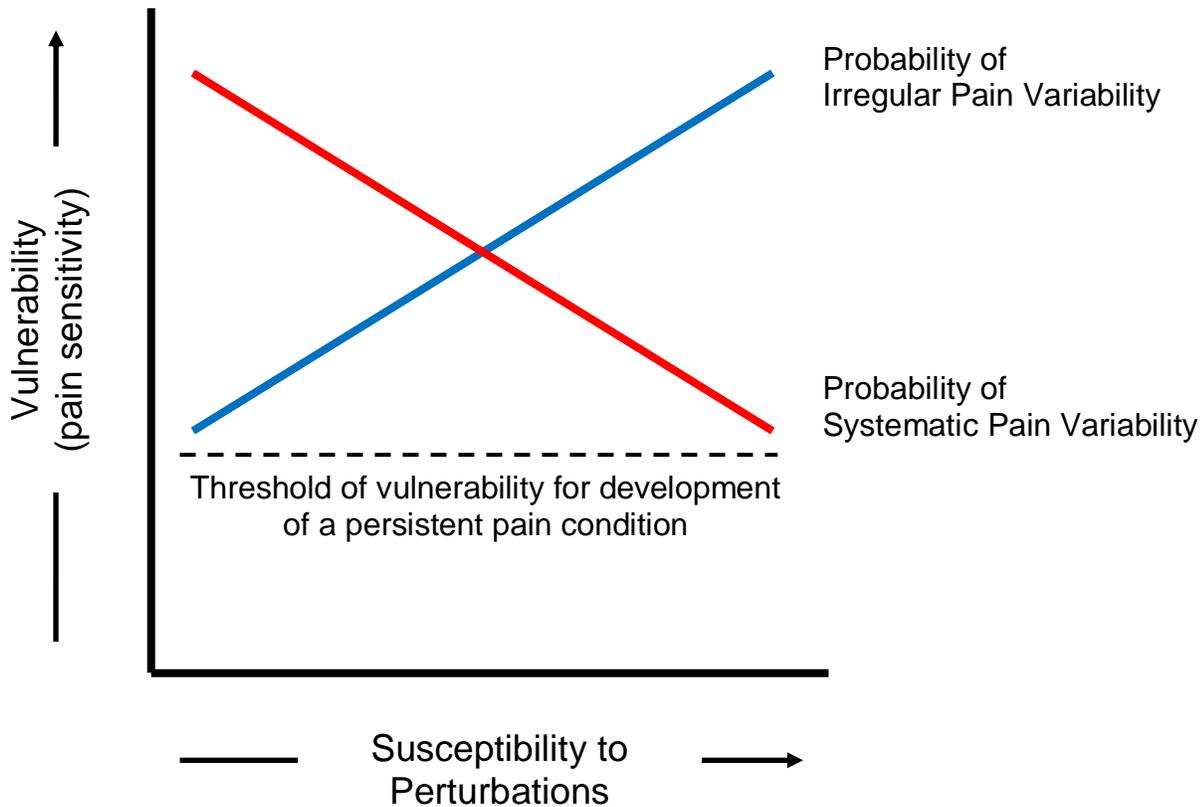
6.5.2.3 Vulnerability perturbation model

The VP model of pain is presented in Figure 6-3. As predisposing vulnerabilities (based on the determinants of health) increase, so too does sensitivity to pain. At a given threshold of vulnerability, an individual will develop a persistent pain condition. This may follow the onset of a diathesis (injury or illness) as identified in the VDS model, or manifest as an idiopathic pain condition. At higher levels of pain sensitivity, individuals will have a higher probability of displaying systematic variability in pain if the susceptibility to perturbations in pain is low. There is an interaction between susceptibility to perturbations and pain sensitivity. As susceptibility to perturbations increases, the probability of having irregular fluctuations in pain increases.

This model assumes a linear relationship between vulnerabilities and pain sensitivity, and linear relationships between vulnerability, susceptibility to perturbations and probabilities of irregular or systematic pain variability. Future testing of the model may identify non-linear relationships between the model components. There is currently no statistical method to

distinguish systematic variability or irregular variability from no variability other than cosinor analysis.

Figure 6-3: Vulnerability Perturbation Model of Pain



However, this method is only able to identify a cosinor pattern of variability and is not able to distinguish between irregular variability and no variability. This model does not take into account pain intensity, magnitude of variability or the pattern or period of systematic pain variability.

6.5.3 Summary

The VP model of pain provides a simple, preliminary framework for examination of factors contributing to the structure of within-day pain variability and inter-individual differences in the temporal dynamics of pain. Pain sensitivity resulting from biological, psychological and social vulnerabilities interacts with susceptibility to perturbations to result in either systematic or

irregular fluctuations in pain. Further research is needed to determine how best to operationalize the construct of susceptibility to perturbations and to statistically determine the probability of systematic or irregular variability. Future research is also needed to test the proposed causal nature of the relationships.

6.6 Strengths and Limitations of the Research

Despite a growing knowledge of the pathophysiology of pain, little has been known about the temporal dynamics of pain in youth. This study contributes to knowledge of the structure and factors influencing within-day pain variability experienced by youth with JIA and non-arthritic pain conditions. The majority of studies examining factors related to pain use single point recall measures which are unable to capture the dynamic nature of pain and are prone to numerous biases. ^(31, 115, 116)

Electronic data capture methods were utilized to assess pain at regular intervals throughout the day to describe and examine factors influencing within-day variability. Although previous studies have commented on within-day variability in pain in youth with JIA, ^(19, 50, 91) to our knowledge, this is the first study to describe and identify factors influencing within-day variability in pain intensity in youth. Previous studies on within-day pain variability aggregated multiple measures or ignored violations of typical analytic methods such as normality of distribution, independence of measures and heteroskedasticity. ⁽¹⁵³⁾ A strength of the current research was in the use of advanced statistical methods that accounted for these challenges. A review of statistical methods with strengths and limitations of each was presented in Chapter 2, Section 3. A limitation of cosinor analysis is the need for imputation of missing data; however, analysis of time series with complete or nearly complete data (no more than 2 missing data points of 21) revealed higher proportions of significant time series. This indicates that the imputation method chosen was a conservative approach to missing data. A limitation of GEE on a polytomous outcome is the lack of production of model fit statistics. Model fit statistics would be produced with GEE on a linear outcome or use of multilevel mixed effects models; however, both of these methods require an outcome variable with an approximately normal distribution. The distribution of pain scores approximated a Tweedie distribution which was resistant to transformations; therefore, categorization of pain intensity was conducted for GEE analysis.

There are no agreed upon cut points for pain categories in adults or children; therefore, categorization was based on previous research⁽²⁷¹⁻²⁷⁷⁾ and on examination of the distribution of the categories. Two cut-point strategies were employed to examine the effects of different pain categorization on the univariate GEE analyses in Study 1. These strategies produced very similar results that did not change the parameter estimates more than 10%. The strategy resulting in a more even distribution of pain scores across the categories was employed; however, this categorization strategy employs a lower boundary between moderate and severe pain (60 on a 0 to 100 VAS) than previous studies. Further research is needed to examine appropriate cut-points for pain categories for youth with JIA and non-JIA persistent pain conditions.

The psychometric properties for the VAS have not been fully examined for electronic diaries in pediatric populations; in particular the reliability (test-retest) and minimal detectable change. Both of these properties would affect the accuracy of scoring and affect variability in pain scores. The influence of slider positioning on reported pain scores has also not been explored.

An advantage of multilevel mixed effects models for analysis is the ability to model individual differences in the relationships of interest. This method may have been able to identify inter-individual differences in relationships between pain and TOD and physical activity. Further research is needed to examine inter-individual differences in the relationships between pain intensity and physical activity.

Additional limitations resulted from the use of secondary data in Study 1, including the choice of variables available for analysis, as well as the timing and frequency of pain measurement. The two studies were complementary. A major strength of the research is that similar descriptive results were found in both studies despite differences in demographic characteristics of the participants, geographical location of the studies, sampling frequency and duration of the observation period. Approximately one quarter of both samples displayed systematic variability in pain intensity that could be described by cosinor analysis. The strength of this finding was supported by the use of two advanced analytic methods. While cosinor analysis and logistic regression were effective for describing one pattern of systematic variability in a portion of the time-series, a TOD effect on pain was confirmed by GEE. A limitation of these methods is that they are unfamiliar to many researchers and clinicians. Further research is

needed to develop methods of analysis that clinicians can use to quantify variability and describe within-day patterns from pain diaries.

Both studies used real time data capture methods ^(352, 353) with electronic diaries using signal prompting and fixed measurement times throughout the day. This is both a strength and limitation in that observations were conducted in the participants' usual environments enabling a longer study observation period than could be feasibly conducted in a lab setting and allowing capture of the typical pain experience. However, we could not restrict extraneous conditions of influence on circadian synchronization, such as diet and timing of meals, sleep times, or light and dark conditions. In order to truly isolate a variable with circadian timing, a desynchronization protocol ⁽¹⁹⁵⁾ would need to be employed over several days. This approach would be impractical and although circadian synchronizers could be standardized, it would not reflect the true lived experience for youth.

Study 2 incorporated a higher frequency of sampling throughout the day with 7 measurements per day. On visual inspection of the time plots, the higher frequency of data capture revealed even greater variability than what was captured with Study 1. It is possible that even higher frequency data capture would reveal additional variability. However, a higher sampling frequency may not provide sufficient additional information in light of the added responder burden of more frequent sampling.

Additional strengths of the research include the development of the electronic diary into an app for the iPod Touch. The code for the app is to be published to an open source software site to allow other programmers access to the source code for further development. Study 2 also used objective measurement of physical activity and developed a novel method for analysis of the short term relationship between physical activity and pain by the use of 2 hour activity windows. In order to examine the data for a U shaped relationship between activity and pain, activity was categorized into a nominal variable. It is possible that this categorization does not reflect true differences in activity behaviour. In addition, the categorization was based on quartiles of activity and inactivity for the group. Individualized calibration of the physical activity categories could have led to different results. This would have been additionally time consuming, as it would require participants to obtain baseline physical activity calibration estimates. The study would have been further strengthened by assessment of physical fitness and

pain sensitivity as both of these variables would have been informative of the relationship between pain and activity. However, accurate assessment of physical fitness is time consuming and requires expensive laboratory equipment and expertise.

There were insufficient numbers of youth with JIA recruited to sufficiently power full model comparisons in Study 2. Although group was significant on univariate analysis on GEE, it was not a significant predictor as a main effect or in interactions in the full model of the combined dataset. In addition, separate JIA and non-JIA GEE analysis resulted in the same main effects models. It was therefore assumed that groups could be combined. However, combined analysis of the two groups presents concerns since the two groups differed in regards to pain intensity and mood. Given sufficient recruitment, group may have emerged as a significant predictor and group differences may have been identified in the relationships between pain intensity, mood and physical activity. The confidence intervals of the odds ratios computed for the logistic regression in Study 2 were very wide, indicating imprecision of the estimates. Findings from this analysis should be interpreted with this limitation in mind.

Due to the ethnic homogeneity of Study 2, the findings cannot be assumed to represent non-English speaking youth, those living in rural and remote communities, or non-Caucasian youth. Oen et al. identified place of residence as a factor of influence on the disease course for youth with JIA,⁽⁷⁶⁾ and it is possible that rural and remote living youth have a different pain experience. Participants for Study 1 and 2 were both recruited from pediatric rheumatology clinical samples. The results of the studies may not be generalizable to youth not in the care of a pediatric rheumatologist. Analysis in both studies was limited to time series in which pain was reported at least once over the observation period. Therefore, these results apply only to youth who experience pain as a component of their illness or injury. Results of Study 2 should be interpreted in light of these limitations.

Although the electronic diaries captured multidimensional aspects of pain, only pain intensity was analyzed in order to narrow the focus of the study. This does not reflect the relative importance of the other components of the pain experience. Further analysis is needed to examine the variability of other aspects of the pain experience, such as pain interference, pain affect, verbal descriptors of pain, body locations in pain and behavioural responses to pain. The relationship between activity level and pain intensity was only examined between the activity

window immediately preceding the pain report. Lagged associations between activity and pain could be assessed, but were not within the scope of this study.

6.7 Implications for Future Research

Within-day variability has been described and explained in two pediatric rheumatology clinical samples. TOD is a significant predictor of pain intensity with differences reported by subtype of arthritis, age, and level of disability. Since present pain has a known biasing effect on recalled pain scores,^(31, 115) researchers utilizing recalled measures of pain are advised to standardize by time of day, or statistically control for time of measurement. Given the extensive within-day variability observed in both samples, researchers are also advised to weigh the benefits and costs of more detailed assessment of pain in consideration of their research question. TOD was also found to interact on the relationship between pain and physical activity. It is recommended that future studies on the short term relationship between pain and activity account for time of day of measurement in the study design or analysis. A strong within-day relationship was identified between mood and pain. It is recommended that future studies with multiple measures of pain account for this relationship in study design or analysis by including a measure of mood in the analysis to control for this effect.

This research has defined and described within-day variability of pain intensity and provided a theoretical framework as a foundation for future studies. Many future directions of research have been suggested. Further work is needed to provide a clinically useful method of analysis for pain diary data. Research is needed to examine the relationship between pain variability and disease course and treatment outcomes. A complex temporal relationship was identified between pain and physical activity which varied by time of day. Predicting which individuals are most at risk for increased pain with physical activity would be an important goal of future research to identify those who suffer most from this barrier to activity participation. Further research is needed to examine the benefits of timing and dose of physical activity interventions in order to guide clinical practice in development of appropriate physical activity interventions. A strong relationship was found between pain and mood which may partially explain within-day irregular fluctuations in pain. However, further research is needed to identify mechanisms of effect, the temporal direction and causal pathways in the relationship between

pain and mood in youth. The VP model of pain presents the construct of susceptibility to perturbations as a factor contributing to inter-individual differences in pain variability. Further research is needed to assess the construct validity, operationalize measurement, and identify factors of influence on susceptibility to perturbations in pain.

Study 2 was ethnically homogeneous, recruited a higher number of males than typical of a pediatric rheumatology case load, and did not include youth from rural and remote communities. Further research is needed to determine if these findings can be extrapolated beyond the characteristics of the study sample.

6.8 Implications for Clinical Practice

These studies provide a greater understanding of the within-day pain experience of youth with JIA and non-arthritic pain conditions. Pain and disability are distressing components of arthritis and other pain conditions that youth may find difficult to understand.⁽⁹²⁾ Clinicians will be able to utilize the findings of these studies when educating patients and their families on the typical pain experience. Pain variability throughout the day is common, and pain changes by time of day, and is related to changes in physical activity, inactivity and mood. Youth may find it reassuring to understand that pain fluctuations are an expected experience that do not necessarily signal further tissue damage. It is important for clinicians to acknowledge and inform patients that higher intensity physical activity may be associated with increased pain, particularly after school and in the evening. Clinicians are advised to clarify for patients the difference between benign flares of pain that are typical of within-day fluctuations and signals of exacerbation of inflammation that warrant medical attention.

Pain intensity fluctuations are related to physical activity and inactivity. Regular participation in physical activity should be recommended for youth with JIA and other pain conditions to obtain general health benefits, improve bone, muscle and joint health and reduce disability.⁽⁸¹⁾ In this study we found that light physical activity was associated with a higher probability of no pain at all times of day. Prolonged sedentariness, particularly in the morning, was associated with a higher probability of moderate or severe pain. Therefore, youth may find it beneficial to avoid prolonged sedentariness in the morning. For example, sedentary time could be interrupted with regular bouts of light activity. Within a 2 hour period, youth may benefit from the accumulation at least 30 minutes of light activity or MVPA. Youth, their parents, or

health care providers should discuss these recommendations with school administrators and employers so that prolonged sedentary positioning can be avoided. Youth may find shorter bouts (10 minutes) of MVPA accumulated throughout the day less painful than a single longer bout. Youth should work with health care providers to develop an activity plan with recommendations for pharmaceutical or non-pharmaceutical pain prevention strategies during activity. Youth may also find it beneficial to engage in physical activity at times of day at which pain is the lowest intensity.

6.9 Conclusions

The findings of these studies contribute to knowledge of the dynamic nature of the pain experience for youth with JIA and non-arthritic pain conditions. Pain variability throughout the day is common, and changes in pain intensity are associated with time of day, physical activity, inactivity and mood. Understanding of the within-day pain experience is necessary for patient education on the expected pain experience. On average, most youth experience higher levels of pain in the morning. This is particularly true for youth with systemic onset arthritis. Females on average exhibit a U shaped pattern to pain with a morning peak, an afternoon trough with a rise in pain intensity in the evening. Males generally exhibit a descending pattern in pain intensity throughout the day with a morning peak and an evening trough. Older youth, and those with systemic onset JIA are more likely to experience systematic pain variability. Irregular fluctuations in pain are related to physical activity and mood. Many other time varying factors not included in this study may also account for these fluctuations. In general there is a U shaped relationship between pain and physical activity that differs by time of day. Light activity is associated with a higher probability of no pain at all times of day. Sedentariness in the morning, and higher activity levels in the evening are associated with a higher probability of higher levels of pain.

An understanding of the short term relationship between pain and physical activity is essential for development of appropriate activity interventions that minimize pain as a barrier to activity participation for this population. This research provides a foundation for further research on the importance of within-day pain variability on treatment response, and disease outcomes. Further research is needed to understand causes of inter-individual differences in pain variability

and susceptibility to perturbations in pain. The VP model of pain is presented as a framework for future research on the temporal dynamics of pain.

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APPENDICES

Appendix A: Juvenile Idiopathic Arthritis Subtype Classification Table

Classification criteria are based on clinical and laboratory features. There are five exclusions which apply differently to each category. ⁽⁷⁾

Exclusions: (application of exclusions is listed for each category)

- a) Psoriasis or a history of psoriasis in the patient or first degree relative.
- b) Arthritis in an HLA-B27 positive male beginning after the 6th birthday.
- c) Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter’s syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative.
- d) The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart.
- e) The presence of systemic JIA in the patient.

JIA Subtype Classification Table

Category	Definition	Exclusions
Systemic Arthritis	Arthritis in one or more joints with or preceded by fever of at least 2 weeks’ duration that is documented to be daily for at least 3 days, and accompanied by one or more of the following: <ol style="list-style-type: none"> 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis 	a b c d
Oligoarthritis	Arthritis affecting one to 4 joints during the first 6 months of disease. Two subcategories are recognized: <ol style="list-style-type: none"> 1. Persistent oligoarthritis: affecting not more than 4 joints throughout the disease course 2. Extended oligoarthritis: affecting a total of more than 4 joints after the first 6 months of disease 	a b c d e
Polyarthritis (Rheumatoid Factor Negative)	Arthritis affecting 5 or more joints during the first six months of disease; a test for RF is negative.	a b c d e
Polyarthritis (Rheumatoid Factor Positive)	Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive	a b c e

<p>Psoriatic Arthritis</p>	<p>Arthritis and psoriasis, or arthritis and at least 2 of the following:</p> <ol style="list-style-type: none"> 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first degree relative 	<p>b c d e</p>
<p>Enthesitis Related Arthritis</p>	<p>Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:</p> <ol style="list-style-type: none"> 1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first degree relative 	<p>a d e</p>
<p>Undifferentiated Arthritis</p>	<p>Arthritis that fulfills criteria in no category or in 2 or more of the above categories.</p>	

Appendix B: Summary of Analytic Methods

Study	Study 1			Study 2		
Method of analysis	2 Stage Regression		GEE	2 Stage Regression		GEE
	Stage 1 Cosinor Analysis	Stage 2 Logistic Regression		Stage 1 Cosinor Analysis	Stage 2 Logistic Regression	
Dependent variable (scale; range)	Pain Intensity (interval; 0-100)	Cosinor Analysis Outcome (nominal; significant/non-significant)	Pain Intensity Categories (ordinal; no pain, mild, moderate, severe)	Pain Intensity (interval; 0-100)	Cosinor Analysis Outcome (nominal; significant/non-significant)	Pain Intensity Categories (ordinal; no pain, mild, moderate, severe)
Independent variables examined	<ul style="list-style-type: none"> • period • frequency • mesor • amplitude • acrophase 	<ul style="list-style-type: none"> • age • sex • disease severity • disease duration • total number active joints • JIA subtype 	<ul style="list-style-type: none"> • time of day • age • sex • disease severity • disease duration • JIA subtype 	<ul style="list-style-type: none"> • period • frequency • mesor • amplitude • acrophase 	<ul style="list-style-type: none"> • age • sex • maturation • BMI • inflammation • disease duration • group (JIA or non-JIA) • cortisol profile 	<ul style="list-style-type: none"> • time of day • mood • physical activity • age • sex • maturation • BMI • inflammation • disease duration • group
Purpose of analysis	Fit a cosine curve to time series data to describe systematic variability (repeating structure) in pain intensity	Examine factors contributing to systematic variability in pain intensity	Determine if pain intensity varies by time of day, demographic or disease variables	As per Study 1		
Strengths of method	<ul style="list-style-type: none"> • highly descriptive parameter estimates produced 		<ul style="list-style-type: none"> • robust method that can handle dependence, 			

	<ul style="list-style-type: none"> • method used to identify within-day pain patterns in adult arthritis pain 	<p>Appropriate method of analysis for dichotomous outcome</p>	<p>non-normal distributions and missing data</p>	
<p>Limitations of method</p>	<ul style="list-style-type: none"> • only time series with a significant zero amplitude test can be described • only identifies cosine rhythm; other repeating patterns not identified • imputations required for missing data 		<ul style="list-style-type: none"> • does not provide descriptive parameter estimates • no model fit statistics produced 	

Appendix C: Recruitment letter

Pediatric Rheumatic Disease Research Laboratory

The Youth Activity and Pain Study

<<Date>>

Dear <<First name of child>> and Parents/Guardians,

We are writing to tell you about a new research study for youth who have pain called, "The Youth Activity and Pain Study." Since, <<first name of child>> was seen at the Rheumatology clinic by Dr. Rosenberg, we thought that you might be interested in taking part.

Some young people with pain notice that their pain changes throughout the day. Sometimes they wake up with pain, or find that they have pain only with certain activities. Sometimes the pain seems to come and go for no reason. We want to see how and why pain changes during the day.

If you agree to help us with this study, we will ask you to answer a few questions on an electronic diary (Apple iPod Touch) seven times a day for four days. An alarm on the diary will remind you to answer the questions. The questions will take about 3 to 5 minutes to complete each time. You will also be asked to wear a motion sensor device (accelerometer) that records how active you are during the day. We want you to participate in all your usual activities during the 4 day study period. Also, twice a day for the same four days we want you to provide a saliva (spit) sample in a small container. This will be used to measure how much of the hormone, cortisol you have in your saliva. You will meet with the study coordinator either before or after a clinic visit, or at another time that is convenient to learn how to use the electronic diary and motion sensor and to answer some questionnaires. At this time we will measure your standing height, sitting height and weight. This meeting will take 45 minutes to one hour. The questionnaires will take about 20-30 minutes to complete. There are two questionnaires for you and two for a parent or guardian to complete. You can complete the questionnaires at the meeting or take them home and fill them in later.

To thank you for taking time to help us with the study, we will give you a gift card for the amount of \$1 for every electronic diary entry you complete. For example, if you complete all of the diary entries, you will get a gift card for \$28 when you return the diary, motion sensor, questionnaires and saliva samples. We will also give you \$2 for filling in the paper questionnaires. You may choose the gift card from a selection of retailers such as Toys R Us or Walmart.

Nothing else will change for you if you choose to be part of the study. If you decide not to, that will not affect your current or future medical treatment. It is up to you to decide whether or not you want to take part.

We hope that you will consider taking part in this study. We think you will find it interesting. If you have any questions or are interested in learning more about this study, please contact Susan Tupper at <<phone number>> or email <<email>>, or call Joan Dietz (research nurse) at <<phone number>>, or email <<email>> and we will answer your questions.

Sincerely yours,

Dr. Alan Rosenberg
966-8112
alan.rosenberg@usask.ca

Susan Tupper, study coordinator
290-0193
susan.tupper@usask.ca

REB Approval Number: Beh 10-45
REB Contact Information: ethics.office@usask.ca

Appendix D: Parent consent form

YOUTH ACTIVITY AND PAIN STUDY - CONSENT FORM

Your child is invited to participate in a research project entitled The Youth Activity and Pain Study. Please read this form carefully, and feel free to ask questions you might have.

Researcher(s):

Dr. Alan Rosenberg, Pediatrics, University of Saskatchewan

(306) 966-8112

Dr. Punam Pahwa, Community Health and Epidemiology, University of Saskatchewan

(306) 966-8300

Susan Tupper, PhD Candidate, Community Health and Epidemiology, University of Saskatchewan

(306) 290-0193

Purpose and Procedure:

This is a study for young people who have pain; youth with arthritis or those with other painful conditions. Some young people with pain notice that it changes throughout the day. Sometimes they wake up with pain, or find that they have pain only with certain activities. Sometimes the pain seems to come and go for no reason. We want to see how and why pain changes during the day for children with and without arthritis.

If you and your child agree to be part of this study, we will ask your child to answer a few questions on an electronic diary (Apple iTouch) 7 times a day for 4 days. These questions will include:

- how much pain he/she has
- where is the pain
- how much does pain gets in the way of what he/she does
- how good or bad is your child's mood
- words that describe what the pain feels like
- how much stiffness he/she has
- how awake or sleepy he/she is
- if he/she took medication, how much it helped or didn't help

An alarm on the diary will remind him/her to answer the questions. This will occur at 8:00 am, and every 2 hours during the day until 8:00 pm. Your child will be given a letter to take to teachers and the principal to tell them about the study since the alarm will sound up to three times during class time on school days. The questions will take about 3 to 5 minutes to complete each time. She/he will also be asked to wear a motion sensor device (Actical accelerometer) that records how active she/he is during the day. She/he will wear the motion sensor on a flexible belt

over her/his right hip beginning on the morning of the first day and ending on the evening of the 4th day. The sensor is water proof and can be worn during bathing. We ask that she/he participates in all of his/her usual activities during the 4 day study period.

Also, twice a day, when your child first wakes up and before she/he goes to sleep for the night, she/he will be asked to provide a saliva (spit) sample by chewing on a cotton swab for two minutes. This will be used to measure how much of the hormone, cortisol, your child has in his/her saliva. You and your child will meet with the study coordinator either before or after a usual visit at the Pediatric Rheumatology Clinic, or at another time that is convenient for you, to learn how to use the electronic diary and motion sensor, to have his/her standing height, sitting height and weight measured, and to answer some paper questionnaires. This meeting will take about 45 minutes to one hour. The questionnaires will take about 25 minutes to complete. You and your child can complete the questionnaires at the meeting, or take them home and fill them in later. There are two brief questionnaires for the child and two brief questionnaires for the parent/guardian. One of the questionnaires for the parents asks about parent's level of education, occupation, family income, housing and ethnicity. This information will be analyzed to see if these aspects of a child's environment influence pain and physical activity. This information will also be used to describe the group of children that agree to participate in the study.

Participation is voluntary. It is up to you and your child to decide whether or not you wish to take part. If you and your child wish to participate, you will be asked to sign this form, and your child will sign a separate form. If you and your child do decide to take part in this study, you or your child are still free to withdraw at any time and without giving any reason for your decision. You and your child may refuse to answer any individual questions. If you and your child do not wish to participate, she/he will not lose the benefit of any medical care to which she/he is entitled or is presently receiving. It will not affect your relationship with Dr. Alan Rosenberg.

The results of the study will be analyzed in aggregate (anonymous), written up in a thesis report and may be presented at national and international conferences, in journal articles, or in news reports.

Potential Benefits: We think your child will find the study interesting. There may be no direct benefit to you or your child for participating in this study. It is hoped the information gained from this study can be used by researchers, doctors and therapists to benefit people with a similar condition in the future. A gift card for the value of \$1 for every electronic diary entry completed will be provided to thank your child for his/her time. If your child completes all of the diary entries, she/he will get \$28 when the diary, motion sensor and saliva samples are returned. We will also give your child \$2 for filling in the paper questionnaires. The maximum possible amount of the gift card is \$30 for full completion of all components of the study. This gift card will be mailed to your child after the diary and questionnaires have been checked for completeness. Even if your child withdraws from the study, he/she will receive the amount of compensation based on the number of diary entries completed. The gift card will be from your child's choice from a selection of stores and restaurants.

Potential Risks: We do not expect your child to experience any risks or discomforts by participating in this study.

Storage of Data: Your name and contact information will be stored in a locked file cabinet in the locked office of Dr. Punam Pahwa at the University of Saskatchewan. This identifying information will be kept until the equipment used in the study is returned and your child has received the gift card. All other data, such as answers to questionnaires will be identified by an anonymous study number. At the completion of your participation, all identifying information about you or your child will be destroyed.

Confidentiality: Your and your child's confidentiality will be respected. No information that discloses your or your child's identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the investigator or his or her designate by representatives of Health Canada, and the University of Saskatchewan Research Ethics Board for the purpose of monitoring the research. However, no records, which identify you or your child by name or initials, will be allowed to leave the investigator's offices. The results of this study may be presented in a scientific meeting or published, but your and your child's identity will not be disclosed.

Right to Withdraw: Your and your child's participation is voluntary, and you can answer only those questions that you are comfortable with. There is no guarantee that you will personally benefit from your involvement. The information that is shared will be held in strict confidence and discussed only with the research team. You may withdraw from the research project for any reason, at any time, without penalty of any sort and if you and your child do not wish to participate, she/he will not lose the benefit of any medical care to which she/he is entitled or is presently receiving. It will not affect your relationship with Dr. Alan Rosenberg. If you or your child withdraws from the research project at any time, you or your child have the right to request that information you have contributed up to that point be withdrawn from the study.

Questions: If you have any questions concerning the research project, please feel free to ask at any point; you are also free to contact the researchers at the numbers provided if you have other questions. This research project has been approved on ethical grounds by the University of Saskatchewan Behavioural Research Ethics Board on April 16, 2010. Any questions regarding your rights as a participant may be addressed to that committee through the Ethics Office (966-2084). Out of town participants may call collect.

Follow-Up or Debriefing: The results of the study will be available by December, 2011 on request from Dr. Alan Rosenberg.

Consent to Participate:

I have read and understood the description provided; I have had an opportunity to ask questions and my/our questions have been answered. I consent to participate in the research project,

understanding that I may withdraw my consent at any time. A copy of this Consent Form has been given to me for my records.

(Name of Participant)

(Name of Parent)

(Date)

(Signature of Parent)

(Signature of Researcher)

Appendix E: Youth assent form

Youth Activity and Pain Study - ASSENT FORM

Why are you here?

We want to tell you about a study we're doing called The Youth Activity and Pain Study. We want to see if you would like to be part of this study. This form tells you about the study. If there is anything you don't understand, please ask your parent or guardian, the doctor, or the study staff.

Researcher(s):

Dr. Alan Rosenberg, Pediatrics, University of Saskatchewan
(306) 966-8112

Dr. Punam Pahwa, Community Health and Epidemiology, University of Saskatchewan
(306) 966-8300

Susan Tupper, Community Health and Epidemiology, University of Saskatchewan
(306) 290-0193

Why are we doing this study?

Some young people with pain notice that it changes during the day. Sometimes they wake up with pain, or find that they have pain only with some things they do. Sometimes the pain seems to come and go for no reason. We want to know what things make pain better and what makes it worse.

What will happen if you take part in the study?

This is some information about the study to help you decide if you want to take part:

1. The study takes four days
2. When you meet with the study staff, you will have your standing height, sitting height and weight measured. You keep your clothes on for this, but take your shoes off.
3. We will train you how to use the electronic diary on the Apple iTouch to answer questions about your pain. We will loan you an iTouch for the four days.
4. Seven times every day for four days you will answer questions on the iTouch. An alarm on the diary will remind you to answer the questions. The questions will take about 3 to 5 minutes to answer each time. We will give you a letter to take to your teachers to tell them about the study so that you may keep the iTouch with you at school. You may have to answer the questions 3 times during school hours; at 10:00 am, noon and 2:00 pm.
5. You will wear a motion sensor that records how active you are for the four days. We want you to do your normal activities.
6. Twice a day, when you first wake up and before you go to sleep for the night, you will chew on a cotton swab for two minutes to give a sample of your spit. The diary will

remind you to do this. This will be used to measure how much of the hormone, cortisol, you have in your body. These samples are stored in plastic tubes in your refrigerator freezer for the four days.

7. There are four paper questionnaires to fill in. You can do the questionnaires at the meeting, or take them home and fill them in later. There are two short questionnaires for your parent/guardian and two for you. It will take about 25 minutes to do all four questionnaires.

Will the study hurt?

There is nothing in this study that will harm you or make you uncomfortable.

What are the good things about taking part in this study?

We think you will like being part of this study. We hope what we learn from doing this study can be used by researchers, doctors and therapists to help other young people like you in the future. To thank you for your time, we will give you a gift card worth \$1 for every electronic diary entry you finish. For example, if you finish all of the diary entries, you will get a gift card for \$28 when the diary, motion sensor and spit samples are returned. We will also give you \$2 for filling in the paper questionnaires. The most you can possibly get is \$30 for filling in all of the diary entries and the questionnaires. Even if you quit the study, you will receive a gift card for the amount that you finished. This gift card will be mailed to you after the diary and questionnaires have been checked. You can choose the gift card from a list of stores and restaurants.

Will it cost you anything to be part of this study?

You do not have to pay anything to be part of this study.

Do you have to be part of the study?

You do not have to take part of this study. If you don't want to be part of this study, just say so. You don't have to give a reason. No one will be upset if you don't want to take part or if you start but then quit the study later. The doctor will still take care of you if you don't want to be part of the study. If you quit the study part way through, you can decide if you want us to keep the information that you give up to that point. If you don't want us to keep that information, we will erase it from our computers and not use it in the study.

Who will know what you did in the study?

Your information will be kept private. No information will be shared that would let anyone know who you are or your answers to questions. Research records and medical records that tell who you are may be checked in the presence of Dr. Rosenberg by workers from Health Canada, and the University of Saskatchewan Research Ethics Board in order to check on the research. However, no records that tell your name or information will be allowed to leave the researcher's

offices. The results of this study will be written up for a thesis report and may be presented at scientific meetings or be published, but your name and personal information will not be shared.

Will you be told about the results of the study?

The results of the study will be ready by December, 2011 from Dr. Rosenberg.

Who do you contact if you have questions about the study?

Please take time to read this information carefully. You can ask the study staff to explain any words that you do not clearly understand. You may ask as many questions as you need. Please feel free to discuss this with your family, friends or family doctor before you decide. If you have any questions or want to know more about this study or have questions during the study, you can contact Susan Tupper at 290-0193.

If you have any concerns about your rights as a research subject and/or experiences while being part of this study, contact the Chair of the University of Saskatchewan Research Ethics Board, at 966-2084. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Research Ethics Board on (insert date).

Assent to Participate:

I have read and understood the description provided; I have had an opportunity to ask questions and my questions have been answered. I agree to participate in the research project, understanding that I may withdraw my assent at any time. A copy of this Assent Form has been given to me for my records.

(Name of Participant) (Date)

(Signature of Participant) (Signature of Researcher)

Appendix F: Study information sheet

Pediatric Rheumatic Disease Research Laboratory

The Youth Activity and Pain Study

Thank you for being part of this study! We hope you find it interesting. If you have any questions about the study, please contact Susan Tupper at 290-0193 or Joan Dietz at 966-2485.

Your part in the study will last four days from _____ to _____. During those four days we ask you to do the following four things.

(1) Electronic Diary

Seven times a day (every 2 hours) the iTouch will alarm. When you hear this alarm, you have 60 minutes to answer the questions. The questions should take about 3 to 5 minutes for you to answer. Please carry the diary with you throughout the day, so you can answer the questions wherever you happen to be. If you miss an alarm for any reason and aren't able to answer the questions in time, that is okay. You can answer the next set of questions when the alarm sounds. If you accidentally lose the diary or have problems with the diary, please contact Susan Tupper at 290-0193 as soon as possible and you will be provided with a new diary to continue the study. You will be provided with a letter for your teachers to tell them about this study so that you can take the iTouch to school.

(2) Motion Sensor

The evening before you begin the study, you will put on the motion sensor belt so that it is over your right hip. You may wear this under or over your clothes; whatever you prefer. You will wear the motion sensor for the full four days of the study. The motion sensor and belt are splash-proof, so you don't need to take it off for a shower, but you cannot wear it underwater in a bath or swimming. The motion sensor is very small and flat, so you don't need to take it off for sleeping, unless you are want to. Any time that you take the belt off, please write down on the Motion Sensor Log the time you took it off, how long it was off and the reason you took it off.

(3) Saliva Samples

Every morning when you wake up, and before you go to bed, the diary will remind you to give a saliva (spit) sample. Some foods and drinks can affect the saliva. Please do not drink any caffeinated drinks (pop, coffee, caffeinated tea) for two hours before you give the sample and do not eat or drink anything for 30 minutes before you give the sample. To give the samples, follow these steps:

- 1 – open the correct tube and remove the cotton swab
- 2 – chew on the swab for 45 seconds
- 3 – place the swab under your tongue to collect any saliva; keep the swab in your mouth for 1 to 2 minutes until it is wet
- 4 – place the swab back in the tube
- 5 – place the tube in the zip-locked bag in your refrigerator freezer

(4) Questionnaires

There are four questionnaires to answer. You can answer these at home or at the clinic.

Demographic Questionnaire – this asks questions about you and your family. This will take about 5 minutes to answer. Your parent or guardian will answer this questionnaire.

Pediatric Quality of Life Questionnaire – this asks questions about how you feel about your life; how satisfied or unsatisfied you are with things about your life. This will take about 5 to 10 minutes to answer.

Childhood Health Assessment Questionnaire – this asks questions about how much difficulty you have with different movements and activities. This will take about 5 to 10 minutes to answer. Your parent or guardian will answer this questionnaire.

Physical Activity Questionnaire – this asks questions about how much physical activity you usually do on a normal day. This will take about 5 to 10 minutes to answer.

(5) Measurements

You will also have some measurements taken of your standing height, weight, and sitting height. We will ask you to take off your shoes for these measures, but you will keep all your clothing on. This will be done when you meet with the study coordinator at the clinic.

You may quit the study at any time for any reason and this will not affect your medical care. If you are unable to continue the study, or wish to stop please contact Susan Tupper at 290-0193 and we will arrange a convenient time to pick up the equipment and the saliva samples.

To thank you for taking time to help us with the study, we will give you a gift card for the amount of \$1 for every electronic diary entry, up to a total of \$28 if you complete all the diary entries. We will give you an additional \$2 for finishing all of the paper questionnaires. The gift-card will be for your choice from a selection of different stores and restaurants. This will be mailed to you after the diary and questionnaires have been checked for completeness.

PICK UP TIME: _____

PICK UP LOCATION: _____

Please call Susan Tupper at 290-0193 or email susan.tupper@usask.ca if you would like to change the time or location.

Thank you for helping us with this study.

We greatly appreciate your time.

Appendix G: PInGo Electronic Diary Training Instructions and Vignette

General Electronic Diary Instructions

Now it's your turn to try the diary on the iPod. We will go through the questions slowly the first time so we can talk about what they mean and how to answer them. Then I'll ask you to answer the questions based on a story so you can practice. Some people find this hard to do and others find it fairly easy. I want to know how it is for you. You can ask me questions at any time as we go through it.

The diary will beep seven times a day; at 8am, 10am, noon, 2pm, 4pm, 6pm and 8pm, so I want you to carry the iPod with you during the day so you can hear the alarm and answer the questions. If the alarm goes and you are too busy to answer the questions, you have up to one hour to finish the questions. But I want you to answer it as close to the alarm as possible. When you answer the questions over the next four days, I want you to do this by yourself. Don't ask your friends, teachers or family to answer them for you. These questions are about how you are feeling, so we want you to answer them. If you have any questions about how to answer the diary questions or are having a problem with the diary, I want you or a parent to call me or email me right away and I'll help you.

Let's take a look. (The practice survey used the morning set of questions)

Once you press the icon to enter the diary you will see three stripes labeled "morning, afternoon and evening." There are only a couple of differences between the three times of day. The correct one for you to use will be lit up. Open the morning survey now and we'll go through the questions.

In the morning and evening, the first page will ask you if you've given the saliva sample as a reminder. Notice that you can't move to the next page of the diary unless you give an answer. Also, once you move to the next page, you can't come back to this one, so think carefully about your answers before you move to the next page.

The first question is asks you to show on these body pictures where you hurt or have pain. You can choose as many locations as you need to show where you hurt or have pain. Why don't you try and touch all the areas where you have hurt or pain right now. *If child or adolescent states they have no painful areas right now, say, "For practice think about the last time you had pain."*

The next question asks you to show how much pain or hurt you have right now. To answer this question, you should move the marker somewhere on this line between "no pain" and "most pain possible" to show how much you hurt. Why don't you try and slide the marker to show how much hurt or pain you have right now. *If child or adolescent states they have no pain right now, say "For practice think about the last time you had pain."*

The next question asks you how upsetting your pain is to you. Sometimes pain can feel unpleasant, yucky or bothersome – this is what we mean by upsetting. To answer this question, you should slide the marker somewhere on this line between “not at all unpleasant” and “very unpleasant” to show how much your pain bothers you right now. Try and slide the marker to show how much your pain bothers you right now. *If child or adolescent states they have no pain right now, say “For practice think about the last time you had pain.”*

The next questions ask how pain has affected the things you do, your walking and sleeping, seeing your friends, and enjoying life. To answer each of these questions you should slide the mark somewhere on the line, between “doesn’t get in the way at all” and “totally gets in the way” to show how much pain has affected or interfered with these things in your life. Now why don’t you try and touch the screen to show how much pain has affected things you do (*or sleep, feelings, seeing friends, enjoying life*) right now. Here is where the questions between each time of day are different. In the afternoon, there is a question asking if pain has gotten in the way of schoolwork and relationships with friends or family and in the evening it asks about pain getting in the way of relationships. *If child or adolescent states they have no pain right now, say, “For practice think about the last time you had pain.”*

The next question asks you to choose words that describe how your pain feels. To answer this question, you should choose the words that best tell how your pain feels right now. These top six words describe the way your pain feels and the bottom five words tell about how your pain has changed since the last time you filled in the diary. Touch the buttons to choose the words that show how your pain feels right now. *If child or adolescent states they have no pain right now, say “For practice think about the last time you had pain.”*

The next question asks you to tell how stiff your joints or muscles feel. To answer this question, you should slide the marker somewhere on this line between “not at all stiff” and “very stiff.” Why don’t you try and slide the marker to show how much stiffness you feel in your joints or muscles right now. *If child or adolescent states they have no stiffness right now, say “For practice think about the last time you had stiffness.”*

The next question asks you to tell how good or bad your mood is right now. To answer this question, you should touch the face that best shows how you are feeling inside from “very bad” to “very good.” It’s not just how your face looks, but how you really feel inside right now. Touch the face now that shows how you are feeling.

The next question asks how awake or sleepy you feel. Even though you are awake, sometimes you feel very energetic and sometimes you feel very tired and sleepy.

To answer this question, you should slide the marker somewhere on this line between “very sleepy” and “very awake” to show how awake or sleepy you feel right now. Slide the marker now to show how sleepy or tired you feel now.

The next question asks if you took any pain medicines to help with your pain since the last time you answered the diary. If you took pain medicine, touch the yes button and another question

will pop up to ask how helpful the medicine was in making your pain feel better. Press the yes button to practice this question. Slide the marker on the line somewhere between “no relief at all” and “complete relief.” “No relief” means the medicine didn’t help at all and “complete relief” means it took all of your pain away. Slide the marker now to show how much your last pain medicine helped with your pain. *If child or adolescent states they have not taken medicine recently, say “For practice think about the last time you took medicine for pain and how much it helped.”* If you took medicine for pain I want you or a parent to fill in what you took on the medication and treatment log. Mark in what medicine you took, how much you took and when you took it.

The next question is similar but it asks about what other types of treatments you tried to help make your pain better. For example, some people try stretches, massage or physiotherapy, or relaxation exercises, hot baths or ice packs to help make pain better. If you tried something other than a medicine to help make pain better, then answer the question about how much it helped. If you tried other things to help with your pain, I want you or a parent to fill in what you did on the medication and treatment log. Mark in what you did and when you did it.

Finally, the diary gives you a chance to write anything down about your pain, the study, your activity or your treatments. Touch the white box and a keyboard will pop up. If you wanted to use a different word to describe your pain that wasn’t on the list before, you can write that word here. You can also write down if you took medicine or other treatments for pain here instead of on the paper log. You don’t have to write anything in here if you don’t want to.

After you’re finished, a box will pop up telling you that you’re done. Press ok and the screen will go blank. Press the home button and it will be returned to the opening screen and it will be ready for the next time.

Practice Vignette

Now let’s practice with the diary again by going through a story.

It’s first thing in the morning. You woke up with your alarm clock and are getting ready for school. You remembered to give your spit sample before brushing your teeth and now the alarm rings on the iPod to remind you to answer the questions. *(youth first answers saliva prompt question – prompt youth to press next button if needed)*

When you first woke up you had pain in your *(name a body location where the youth typically feels pain)*, and now that you’re moving around a bit you also feel it in your *(name another location that youth feels pain. Wait for youth to touch the correct body location and move to the next page. Remind the child that they can’t move backward in the survey, so to think carefully about the body locations in pain. If necessary, prompt child again to press the next button to move forward in the survey).*

When you first woke up you had a lot of pain in your *(name primary body part)* Where would you put the mark to show how much pain you have? *(marker should be above the midway line)*

Where would you slide the marker if I said that you only had a little bit of pain? (*youth should slide marker to the left indicating a lower level of pain.*) Show me again where you would slide the marker if you were having a lot of pain (*youth should slide the marker to the right indicating a higher level of pain.*) Okay, let's move to the next question.

Even though you were having a lot of pain, it isn't really bothering you. Where would you put the mark to show how unpleasant your pain is? (*marker should be below the midway line*) Where would you slide the marker if I said that it was bothering you more than it normally did? (*youth should slide marker to the right indicating a higher level of unpleasantness*)

You have a medium amount of pain and it's not really bothering you. It's also not getting in the way of doing things. Where would you slide the mark to show how much your pain is interfering or getting in the way of you doing things? (*marker should be below the midway line*) Where would you slide the marker if I said that it was really getting in the way of doing things? (*youth should slide marker to the right indicating a higher level of general interference*)

(repeat VAS procedure for other interference questions starting with a high or low level and having youth change score in the opposite direction – determine if youth is able to select appropriate starting point and direction of change.)

Now we're at the page where you get to choose the words that best describe how your pain feels. You can describe your pain any way you want right now.

(repeat VAS procedure for stiffness question)

When you woke up you were feeling not really in a good or bad mood – just kind of neutral. What face would you choose to show feeling that way? (*youth should select neutral face*) What face would you choose if I said you woke up feeling happy? (*youth should select one of the positive valence faces*) What face would you choose if I said you woke up feeling sad, angry or depressed? (*youth should select one of the negative valence faces*)

Now you're feeling really energetic and ready to go. Where would you slide the marker to show feeling energetic? (*youth should slide the marker to the right of the midway line*) Where would you slide the marker if I said you were feeling tired, like you just needed to sit down for a rest or put your head down on your desk? (*youth should slide the marker to the left of the midway line to indicate low activation*)

You didn't use any medication this morning for pain. (*youth should select "no" button and move to the next page*) But you did some stretches to try to make the pain in your (*name body part*) better. The stretches helped a little. Where would you slide the marker to show that the stretches helped a bit? (*youth should place the marker to the left of midline*)

Now you can type whatever you want in the open box.

Do you have any questions?

Appendix H: Letter to school personnel



To Whom It May Concern:

_____ is enrolled in a research study at the University of Saskatchewan entitled the *Youth Activity and Pain Study*. We will be collecting information several times throughout the day using a brief questionnaire on an Apple iPod Touch. Three of the questionnaire times occur during school hours; at 10am, noon and 2pm. A brief alarm will ring to prompt the student to answer the questionnaire. The questionnaire takes approximately 3-5 minutes to complete. Students have 60 minutes to begin the questionnaire, thereby allowing a certain amount of flexibility for completing the questionnaire.

We ask that _____ be allowed to keep the iPod Touch at school in order to complete these questionnaires.

The iPod Touch has been programmed to block all other applications. The student will not be able to play games, access the internet or use the iPod Touch for any purpose other than the study questionnaire. This will occur on the following days:

_____.

The student will also wear an accelerometer (motion sensing device) which can be worn under the clothing and will not interfere with school participation.

Please do not hesitate to contact us for more information regarding this study if you have any concerns regarding your student's participation.

Sincerely,

Dr. Alan Rosenberg
966-8112
alan.rosenberg@usask.ca

Susan Tupper
290-0193
susan.tupper@usask.ca

Study Protocol Number: Beh 10-45

Appendix I: Accelerometer removal log

MOTION SENSOR LOG

Please fill in the table if you remove the motion sensor for any reason

Date	Time removed	Reason for Removal	Length of Time Motion Sensor Removed or Time Returned

Use back of page if needed

ID #: _____

Appendix J: Clinical data collection form

Clinical Data Collection Form

Name:

ID#:

Age:

Birthdate:

Sex:

Disease Subtype/diagnosis:

Duration of disease (years since diagnosis):

ESR:

Date of last ESR:

Appendix K: Thank you and gift card letter



Pediatric Rheumatic Disease Research Laboratory **The Youth Activity and Pain Study**

<<Date>>

Dear <<participant first name>>,

Thank you for being part of our research study. To thank you for all the time you have given to be part of this study we are enclosing a gift card from <<vendor>> for <<amount>>.

You completed <<number>> of the iPod diary entries. This completes your participation in the study.

We appreciate all of your help and hope you enjoyed being part of the study. The results of the study will be available from Dr. Rosenberg by December, 2011.

Sincerely yours,

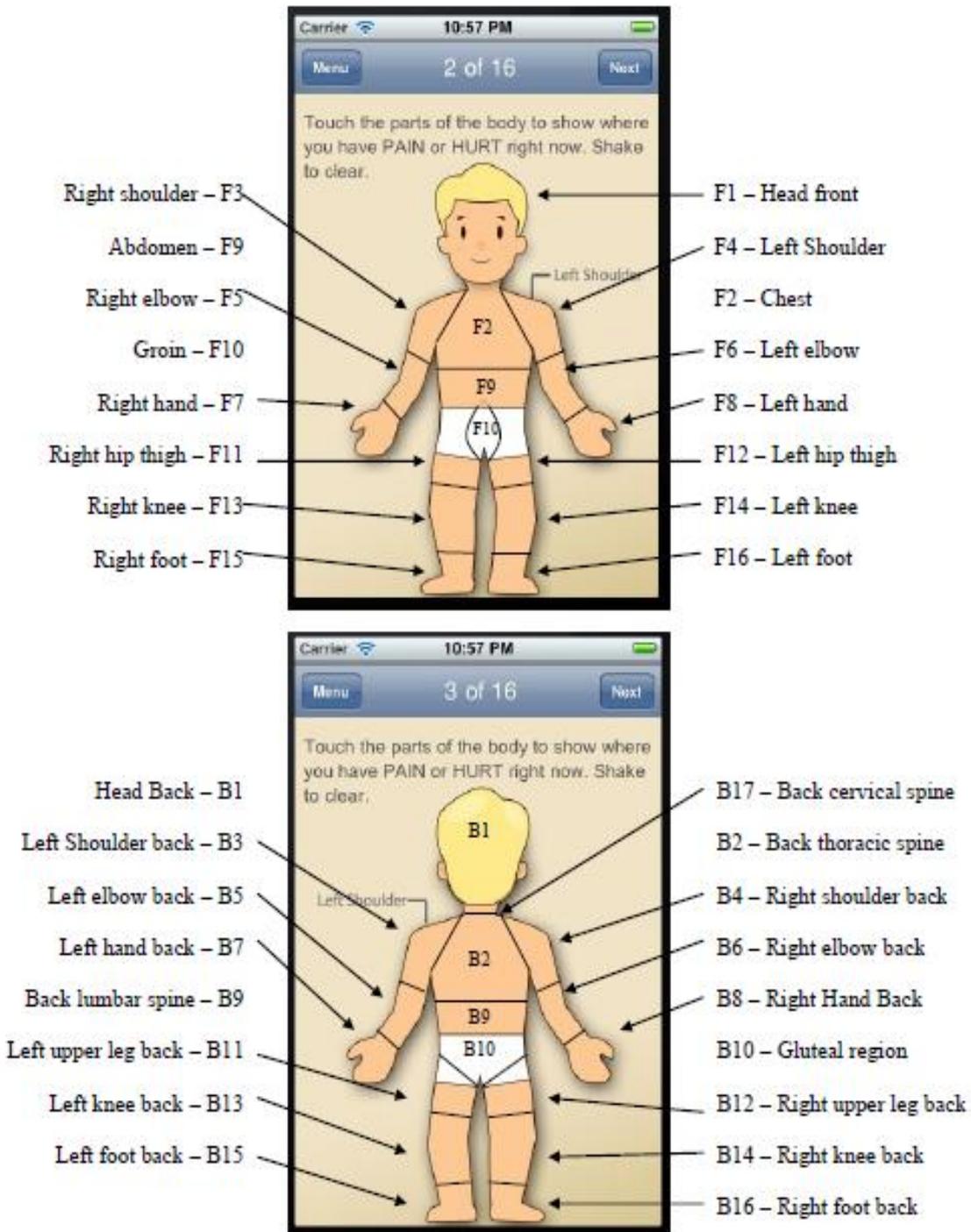
Dr. Alan Rosenberg
Pediatric Rheumatologist

Susan Tupper
Study Coordinator

Appendix L: PInGo afternoon and evening survey questions

Page Number	Survey	
	Afternoon	Evening
1	Body map front	Saliva sample prompt
2	Body map back	Body map front
3	Pain intensity VAS	Body map back
4	Pain affect VAS	Pain intensity VAS
5	Pain interference – general	Pain affect VAS
6	Pain interference – walking	Pain interference – general
7	Pain interference – schoolwork	Pain interference – walking
8	Pain interference – relationships	Pain interference – relationships
9	Pain interference – enjoying life	Pain interference – enjoying life
10	Descriptor words checklist	Descriptor words checklist
11	Stiffness VAS	Stiffness VAS
12	Emotional valence	Emotional valence
13	Emotional activation	Emotional activation
14	Pharmacological interventions	Pharmacological interventions
15	Non-pharmacological interventions	Non-pharmacological interventions
16	Open field	Open field

Appendix M: PInGo body map response options



Appendix N: PInGo faces scale for emotional valence



Appendix O: Treatment log

Treatment Log

ID #: _____

Some medications and other treatments may affect your child’s pain. We would like to know what your child has used **to help with pain** during the day. Below is a list of some of the common medications and treatments that you may have tried. Please list all treatments, even if they are not on this list. This list is only to remind you of things you may have used. **Please do not start any new treatments unless you have discussed it first with Dr. Rosenberg or your family doctor.** Some of these treatments may have negative side-effects with the treatments that have been recommended for you.

Medications:

- Acetaminophen (Tylenol)
- Ibuprofen (Advil, Motrin)
- Naproxen (Naprosyn)
- Sulfasalazine
- Celebrex
- Aspirin
- Methotrexate
- Enbrel
- Remicade

Non-Medical Treatments:

- Massage
- Stretches
- Heat – eg. hot-pack
- Cold – eg. ice-pack
- TENS unit
- Herbal remedies:
 - Topical (eg. Capsacin)
 - Oral (eg. Herbal supplements)
- Acupuncture
- Relaxation or Imagery

Date	Time of day treatment taken or tried	Name of treatment; amount or duration
Example 1: Sept. 28, 2009	8:30 am	Tylenol; 1 extra-strength
Example 2: Sept. 28, 2009	7:00 pm	Massage on lower leg; 10 minutes

Please use extra pages if needed

Appendix P: Demographic questionnaire

(Parent)

**Youth Activity and Pain Study
DEMOGRAPHIC QUESTIONNAIRE**

ID #: _____

This questionnaire asks some background information about your family to help us understand more about children who have pain. The “participant” is the child that is enrolled in the study. Please do not put your name on this questionnaire. The answers you give will be kept confidential.

1. PARTICIPANT INFORMATION

Participant’s birth date _____ / _____ / _____ Participant’s sex (circle) Female / Male
(year) (month) (day)

2. PARENT EDUCATION

Participant’s **mother’s** highest level of education is: (check only one)

- Professional training or Graduate School (MA, MS, ME, MD, PhD, LLD, etc).....
- University or College graduate.....
- Some University or College education (degree/diploma not completed).....
- High School Graduate.....
- Ten to eleven years of school (part high school).....
- Seven to nine years of school.....
- Less than seven years of school.....

Participant’s **father’s** highest level of education is: (check only one)

- Professional training or Graduate School (MA, MS, ME, MD, PhD, LLD, etc).....
- University or College graduate.....
- Some University or College education (degree/diploma not completed).....
- High School Graduate.....
- Ten to eleven years of school (part high school).....
- Seven to nine years of school.....
- Less than seven years of school.....

3. HOUSING

The home that the participant lives in is:

- Owned by participant’s family Detached House.....
- Rented by participant’s family..... Apartment
- Other Townhouse/condominium

If ‘other’ please give details _____

4. PARENT OCCUPATION

Mother’s Occupation

Father’s Occupation

ID #: _____

5. FAMILY INCOME

Total family income before taxes is (check one):

- > \$90,000
- \$70,000 to \$89,999
- \$50,000 to \$69,999
- \$30,000 to \$49,000
- < \$ 29,999
- I do not wish to answer this question

6. ETHNICITY

Participant's mother's ethnicity/race is: (check only one)

- | | |
|--|--|
| White/North European..... <input type="checkbox"/> | Arab <input type="checkbox"/> |
| Aboriginal (First Nation, Métis, Inuit) <input type="checkbox"/> | West Asian <input type="checkbox"/> |
| Chinese <input type="checkbox"/> | Korean..... <input type="checkbox"/> |
| South Asian (East Indian, Pakistani, etc.)..... <input type="checkbox"/> | Japanese <input type="checkbox"/> |
| Black <input type="checkbox"/> | Mixed parentage <input type="checkbox"/> |
| Filipino <input type="checkbox"/> | Not known <input type="checkbox"/> |
| Latin American <input type="checkbox"/> | Other (Please describe) <input type="checkbox"/> |
| Southeast Asian (Iranian, Afghan, etc.) <input type="checkbox"/> | |

I do not wish to answer this question.....

Participant's father's ethnicity/race is: (check only one)

- | | |
|--|--|
| White/North European..... <input type="checkbox"/> | Arab <input type="checkbox"/> |
| Aboriginal (First Nation, Métis, Inuit) <input type="checkbox"/> | West Asian <input type="checkbox"/> |
| Chinese <input type="checkbox"/> | Korean..... <input type="checkbox"/> |
| South Asian (East Indian, Pakistani, etc.)..... <input type="checkbox"/> | Japanese <input type="checkbox"/> |
| Black <input type="checkbox"/> | Mixed parentage <input type="checkbox"/> |
| Filipino <input type="checkbox"/> | Not known <input type="checkbox"/> |
| Latin American <input type="checkbox"/> | Other (Please describe) <input type="checkbox"/> |
| Southeast Asian (Iranian, Afghan, etc.) <input type="checkbox"/> | |

I do not wish to answer this question.....

THANK YOU VERY MUCH FOR YOUR PARTICIPATION

WE GREATLY APPRECIATE YOUR TIME.

Appendix Q: Childhood Health Assessment Questionnaire

CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE

1990 © Original version Singh G et al. 1998 © Cross-cultural version Woo P, Murray P, Nugent J

We are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please tick the one response which best describes his/her usual activities OVER THE PAST WEEK. **ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS.** If most children at your child's age are not expected to do a certain activity, please mark it as 'not applicable'. For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young, but not because he/she is **RESTRICTED BY ILLNESS**, please mark it as 'not applicable'.

	Without ANY <u>Difficulty</u>	With SOME <u>difficulty</u>	With MUCH <u>difficulty</u>	UNABLE <u>to do</u>	Not <u>applicable</u>
DRESSING & PERSONAL CARE					
Is your child able to:					
- Dress, including tying shoelaces and doing buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Shampoo his/her hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Remove socks?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Cut fingernails?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
GETTING UP					
Is your child able to:					
- stand up from a low chair or floor?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Get in and out of bed ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EATING					
Is your child able to:					
- Cut his/her own meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Lift a cup or glass to mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Open a new cereal box?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
WALKING					
Is your child able to					
- Walk outside on flat ground?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Climb up five steps?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

* Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:

Devices used for dressing (button hook, zip pull, long-handled shoe horn, etc.)	<input type="checkbox"/>			
Walking stick	<input type="checkbox"/>			
Walking frame	<input type="checkbox"/>	Built up pencil or special utensils		<input type="checkbox"/>
Crutches	<input type="checkbox"/>	Special or built up chair		<input type="checkbox"/>
Wheelchair	<input type="checkbox"/>	Other _____		<input type="checkbox"/>

* Please tick any categories for which your child usually needs help from another person **BECAUSE OF PAIN OR ILLNESS**:

Dressing and personal care	<input type="checkbox"/>	Eating	<input type="checkbox"/>
Getting up	<input type="checkbox"/>	Walking	<input type="checkbox"/>

	<u>Without ANY Difficulty</u>	<u>With SOME Difficulty</u>	<u>With MUCH Difficulty</u>	<u>UNABLE To do</u>	<u>Not Applicable</u>
HYGIENE					
Is your child able to:					
- Wash and dry your entire body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Take a bath (get in and get out)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Get on and off the toilet or potty?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Brush teeth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- Comb/brush hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

REACH					
Is your child able to:					
- Reach and get down a heavy object such as a large game or books from just above his/her head?	<input type="checkbox"/>				
- Bend down to pick up clothing or a piece of paper from the floor?	<input type="checkbox"/>				
- Pull on a jumper over his/her head?	<input type="checkbox"/>				
- Turn neck to look back over shoulder?	<input type="checkbox"/>				

GRIP					
Is your child able to:					
- Write or scribble with pen or pencil?	<input type="checkbox"/>				
- Open car doors?	<input type="checkbox"/>				
- Open jars, which have been previously opened?	<input type="checkbox"/>				
Turn taps on and off?	<input type="checkbox"/>				
- Push open a door when you have to turn a door knob?	<input type="checkbox"/>				

ACTIVITIES					
Is your child able to:					
- Run errands and shop?	<input type="checkbox"/>				
- Get in and out of a car, toy car or school bus?	<input type="checkbox"/>				
- Ride bike or tricycle?	<input type="checkbox"/>				
- Do household chores (eg. Wash dishes, take out rubbish, hovering)	<input type="checkbox"/>				
- Run?	<input type="checkbox"/>				

* Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:

Raised toilet seat	<input type="checkbox"/>	Bath rail	<input type="checkbox"/>
Bath seat	<input type="checkbox"/>	Long-handled appliances for reach	<input type="checkbox"/>
Jar opener (for jars previously opened)	<input type="checkbox"/>	Long-handled appliances in bathroom	<input type="checkbox"/>

* Please tick any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:

Hygiene	<input type="checkbox"/>	Gripping and opening things	<input type="checkbox"/>
Reach	<input type="checkbox"/>	Errands and chores	<input type="checkbox"/>

PAIN : We are also interested in learning whether or not your child has been affected by pain because of his or her illness. How much pain do you think your child has had IN THE PAST WEEK? Place a mark on the line below, to indicate the severity of the pain

No pain 0 |-----| 100 Very severe pain

GENERAL EVALUATION: Considering all the ways that arthritis affects your child, rate how he/she is doing by placing a single mark on the line below.

Very well 0 |-----| 100 Very poor

Appendix R: Physical Activity Questionnaire for Older Children (PAQ-C)

Physical Activity Questionnaire (Elementary School)

In this section we would like to collect information about your level of physical activity in the last 7 days.

Remember:

1. There are no right and wrong answers — this is not a test.
2. Please answer all the questions as honestly and accurately as you can — this is very important.

1. Physical activity in your spare time: Have you done any of the following activities in the past 7 days (last week)? If yes, how many times? (Mark only one circle per row.)

	No	1-2	3-4	5-6	7 times or more
Skipping	<input type="radio"/>				
Rowing/canoeing	<input type="radio"/>				
In-line skating	<input type="radio"/>				
Tag	<input type="radio"/>				
Walking for exercise	<input type="radio"/>				
Bicycling	<input type="radio"/>				
Jogging or running	<input type="radio"/>				
Aerobics	<input type="radio"/>				
Swimming	<input type="radio"/>				
Baseball, softball	<input type="radio"/>				
Dance	<input type="radio"/>				
Football	<input type="radio"/>				
Badminton	<input type="radio"/>				
Skateboarding	<input type="radio"/>				
Soccer	<input type="radio"/>				
Street hockey	<input type="radio"/>				
Volleyball	<input type="radio"/>				
Floor hockey	<input type="radio"/>				
Basketball	<input type="radio"/>				
Ice skating	<input type="radio"/>				
Cross-country skiing	<input type="radio"/>				
Ice hockey/ringette	<input type="radio"/>				
Other:					
.....	<input type="radio"/>				
.....	<input type="radio"/>				

2. In the last 7 days, during your physical education (PE) classes, how often were you very active (playing hard, running, jumping, throwing)? (Check one only.)

- I don't do PE
- Hardly ever
- Sometimes
- Quite often
- Always

3. In the last 7 days, what did you do most of the time *at recess*? (Check one only.)

- Sat down (talking, reading, doing schoolwork)...
- Stood around or walked around
- Ran or played a little bit
- Ran around and played quite a bit
- Ran and played hard most of the time

4. In the last 7 days, what did you normally do *at lunch* (besides eating lunch)? (Check one only.)

- Sat down (talking, reading, doing schoolwork)...
- Stood around or walked around
- Ran or played a little bit
- Ran around and played quite a bit
- Ran and played hard most of the time

5. In the last 7 days, on how many days *right after school*, did you do sports, dance, or play games in which you were very active? (Check one only.)

- None
- 1 time last week
- 2 or 3 times last week
- 4 times last week
- 5 times last week

6. In the last 7 days, on how many *evenings* did you do sports, dance, or play games in which you were very active? (Check one only.)

- None
- 1 time last week
- 2 or 3 times last week
- 4 or 5 times last week
- 6 or 7 times last week

7. On the last weekend, how many times did you do sports, dance, or play games in which you were very active? (Check one only.)

- None
- 1 time
- 2 — 3 times
- 4 — 5 times
- 6 or more times

8. Which one of the following describes you best for the last 7 days? Read all five statements before deciding on the one answer that describes you.

- A. All or most of my free time was spent doing things that involve little physical effort
- B. I sometimes (1 — 2 times last week) did physical things in my free time (e.g. played sports, went running, swimming, bike riding, did aerobics)
- C. I often (3 — 4 times last week) did physical things in my free time
- D. I quite often (5 — 6 times last week) did physical things in my free time ...
- E. I very often (7 or more times last week) did physical things in my free time .

9. Mark how often you did physical activity (like playing sports, games, doing dance, or any other physical activity) for each day last week.

	None	Little bit	Medium	Often	Very often
Monday	<input type="radio"/>				
Tuesday	<input type="radio"/>				
Wednesday	<input type="radio"/>				
Thursday	<input type="radio"/>				
Friday	<input type="radio"/>				
Saturday	<input type="radio"/>				
Sunday	<input type="radio"/>				

10. Were you sick last week, or did anything prevent you from doing your normal physical activities? (Check one.)

- Yes
- No

If Yes, what prevented you? _____

11. What additional activities or chores have you participated in at home in the last 7 days? (Please use back of page if you need additional space.)

Appendix S: Physical Activity Questionnaire for Adolescents (PAQ-A)

Physical Activity Questionnaire (High School)

Name: _____

Age: _____

Sex: M _____ F _____

Grade: _____

Teacher: _____

We are trying to find out about your level of physical activity from *the last 7 days* (in the last week). This includes sports or dance that make you sweat or make your legs feel tired, or games that make you breathe hard, like tag, skipping, running, climbing, and others.

Remember:

3. There are no right and wrong answers — this is not a test.
4. Please answer all the questions as honestly and accurately as you can — this is very important.

1. Physical activity in your spare time: Have you done any of the following activities in the past 7 days (last week)? If yes, how many times? (Mark only one circle per row.)

	No	1-2	3-4	5-6	7 times or more
Skipping	<input type="radio"/>				
Rowing/canoeing	<input type="radio"/>				
In-line skating	<input type="radio"/>				
Tag	<input type="radio"/>				
Walking for exercise	<input type="radio"/>				
Bicycling	<input type="radio"/>				
Jogging or running	<input type="radio"/>				
Aerobics	<input type="radio"/>				
Swimming	<input type="radio"/>				
Baseball, softball	<input type="radio"/>				
Dance	<input type="radio"/>				
Football	<input type="radio"/>				
Badminton	<input type="radio"/>				
Skateboarding	<input type="radio"/>				
Soccer	<input type="radio"/>				
Street hockey	<input type="radio"/>				
Volleyball	<input type="radio"/>				
Floor hockey	<input type="radio"/>				
Basketball	<input type="radio"/>				
Ice skating	<input type="radio"/>				
Cross-country skiing	<input type="radio"/>				
Ice hockey/ringette	<input type="radio"/>				
Other:					
.....	<input type="radio"/>				
.....	<input type="radio"/>				

2. In the last 7 days, during your physical education (PE) classes, how often were you very active (playing hard, running, jumping, throwing)? (Check one only.)

- I don't do PE
- Hardly ever
- Sometimes
- Quite often
- Always

3. In the last 7 days, what did you normally do *at lunch* (besides eating lunch)? (Check one only.)

- Sat down (talking, reading, doing schoolwork).....
- Stood around or walked around
- Ran or played a little bit
- Ran around and played quite a bit
- Ran and played hard most of the time

4. In the last 7 days, on how many days *right after school*, did you do sports, dance, or play games in which you were very active? (Check one only.)

- None
- 1 time last week
- 2 or 3 times last week
- 4 times last week
- 5 times last week

5. In the last 7 days, on how many *evenings* did you do sports, dance, or play games in which you were very active? (Check one only.)

- None
- 1 time last week
- 2 or 3 times last week
- 4 or 5 last week
- 6 or 7 times last week

6. *On the last weekend*, how many times did you do sports, dance, or play games in which you were very active? (Check one only.)

- None
- 1 time
- 2 — 3 times
- 4 — 5 times
- 6 or more times

7. Which *one* of the following describes you best for the last 7 days? Read *all five* statements before deciding on the *one* answer that describes you.

- F. All or most of my free time was spent doing things that involve little physical effort
- G. I sometimes (1 — 2 times last week) did physical things in my free time (e.g. played sports, went running, swimming, bike riding, did aerobics)
- H. I often (3 — 4 times last week) did physical things in my free time
- I. I quite often (5 — 6 times last week) did physical things in my free time
- J. I very often (7 or more times last week) did physical things in my free time

8. Mark how often you did physical activity (like playing sports, games, doing dance, or any other physical activity) for each day last week.

	None	Little bit	Medium	Often	Very often
Monday	<input type="radio"/>				
Tuesday	<input type="radio"/>				
Wednesday	<input type="radio"/>				
Thursday	<input type="radio"/>				
Friday	<input type="radio"/>				
Saturday	<input type="radio"/>				
Sunday	<input type="radio"/>				

9. Were you sick last week, or did anything prevent you from doing your normal physical activities? (Check one.)

- Yes
- No

If Yes, what prevented you? _____