EXAMINING THE RELATIONSHIP BETWEEN SELF-PERCEIVED HEALTH AND WELL-BEING AND PHYSICAL ACTIVITY AND FITNESS IN CHILDREN WITH A CHRONIC CONDITION

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TITLE**:** Examining the relationship between self-perceived health and well-being and physical activity and fitness in children with a chronic condition

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ABSTRACT

Habitual physical activity and fitness are well-established as independent predictors of health in both children and adults. Chronic inflammatory conditions in children have been shown to negatively impact participation and maintenance of physical activity in childhood which can lead to a reduction in fitness. Juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD) are two of the most common childhood chronic conditions, both of which are characterized by inflammation. Alarmingly, even during remission, physical activity and fitness levels are reduced and sickness behaviours persist in these children. As such, it is thought that psychosocial measures, such as self-perceived health and well-being, may have a stronger association with decreased physical activity and fitness levels in this population as compared to healthy controls. The purpose of this project was to examine the relationship between self-perceived health and well-being and physical activity and fitness in children with JIA or IBD.

In total, 58 children (32 girls, 26 boys) between the ages of 7 and 17 years with a single diagnosis of either JIA or IBD, and healthy controls were recruited. They completed measures of anthropometry, body composition, physical activity, as well as fitness (aerobic and muscle strength). Questionnaires regarding perceived health and well-being were also completed, and blood samples were obtained to measure specific markers of inflammation.

Children with JIA or IBD were found to engage in significantly less moderate-to-vigorous physical activity (MVPA) relative to healthy controls ($t = -1.977$, $p = 0.040$). A linear regression established that MVPA, when expressed as an average of minutes per

day, could statistically significantly predict self-perceived health, $F(1,50) = 6.516$, $p = 0.014$, where MVPA accounted for 11.5% of the explained variability in self-perceived health. This was no longer significant with the controls age, sex, and body fat percentage added into the model. Linear regression models showed that fitness was more predictive of self-perceived well-being, as seen with relative VO_2 peak, $F(1,38) = 6.683$, $p = 0.014$, where relative VO_2 peak accounted for 15% of the variability with self-perceived well-being. Furthermore, composite isometric strength expressed relative to body mass was able to significantly predict a composite blood inflammatory marker score, $F(1,49) = 4.447$, $p = 0.040$, where a relative composite isometric strength score accounted for 8.3% of the variability in a composite inflammatory blood marker score.

Our findings indicate weak but significant predictive power for physical activity and fitness variables with regards to self-perceived health and well-being. Therefore, it may be important to explore ways to increase self-perceived health and well-being in children with JIA or IBD in order to improve physical activity participation and fitness.

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LIST OF ABBREVIATIONS AND SYMBOLS

%WT	percentage of wear time
BMI	body mass index
CD	Crohn's disease
CHAMPION	Cardiovascular Health AssessMent in Pediatric chronic Inflammatory ConditiONs
CHAQ	Child Health Assessment Questionnaire
CRP	C-reactive protein
CSEP	Canadian Society for Exercise Physiology
CV	coefficient of variation
CVD	cardiovascular disease
ELISA	enzyme-linked immunosorbent assay
FFM	fat free mass
HR	heart rate
IBD	inflammatory bowel disease
IC	indeterminate colitis
IgE	immunoglobulin E
IL-6	interleukin 6
IM	inflammatory markers
JADAS	Juvenile Arthritis Disease Activity Score
JIA	juvenile idiopathic arthritis
K-W	Kuskal-Wallis test
LPA	light physical activity

MIBDI	Manitoba IBD Index
MVPA	moderate to vigorous physical activity
NSAID	non-steroidal anti-inflammatory drug
PA	physical activity
PACER	progressive aerobic cardiovascular endurance run
PAQ-C	Physical Activity Questionnaire for Children
PCDAI	Pediatric Crohn's Disease Activity
PH	self-perceived health
PUCDAI	Pediatric Ulcerative Colitis Disease Activity Index
PWB	self-perceived well-being
RER	respiratory exchange ratio
RF	rheumatoid factor
TNF- α	tumor necrosis factor alpha
TPA	total physical activity
UC	ulcerative colitis
VO_2 max/peak	maximal/peak oxygen uptake
W	watts
WHO	World Health Organization

CHAPTER 1: LITERATURE REVIEW

1.1 Epidemiology and Clinical Features of Juvenile Idiopathic Arthritis and Inflammatory Bowel Disease

1.1.1 Juvenile Idiopathic Arthritis

Juvenile Idiopathic Arthritis (JIA) is the most common chronic childhood rheumatic disease with a prevalence of 1 in 1000 children under 16 years of age (Prakken, Albani, & Martini, 2011). Its incidence is 12 in 100 000 in North America. It is an autoimmune disease related to the joints and it is not isolated to a single presentation. Rather, it encompasses all forms of swelling in one or more joint(s) of unknown origin that begins before the age of 16 and persists for longer than 6 weeks (Prakken, Albani, & Martini, 2011). The International League of Associations for Rheumatology has differentiated 6 subtypes of JIA with a wide range of features, as outlined in Table 1. A common misconception is that JIA is similar to arthritis in adulthood, however, it is much more heterogeneous. Although both are considered autoimmune conditions, JIA can affect growth and persist into adulthood, resulting in inflammation and joint damage that can lead to long term morbidity and even physical disability (Harrold et al., 2013). Some typical symptoms include joint pain and swelling, joint stiffness in the morning, and difficulty doing activities of daily living. In addition, patients often experience unpredictable changes in symptoms due to periods of remission and flare-ups (Carrasco, 2015).

Table 1: Subtypes of JIA according to the International League of Associations for Rheumatology classification criteria. Frequencies are a percentage of all JIA cases (Barut et al, 2017; Ravelli & Martini, 2007; Houghton, 2012; Petty et al., 2004).

JIA Subtype	Feature	Frequency
Systemic arthritis	≥ 1 joint(s) affected; Recurrent fever and rash, systemic inflammation	10-20%
Oligoarticular juvenile idiopathic arthritis	≤ 4 joints affected; Commonly affects knee, ankle, wrist, and/or elbow joints; much more common in F than M	50-60%
RF-positive polyarthritis	≥ 5 joints affected; Analogue of adult rheumatoid arthritis	2-10%
RF-negative polyarthritis	≥ 5 joints; Symmetrical arthritis of the small joints of the hands and fingers	11-30%
Psoriatic arthritis	Psoriatic rash, accompanied by arthritis common in small joints, knees, and ankles, with nail pitting, and dactylitis	3-10%
Enthesitis-related arthritis	Enthesitis and arthritis of large joints of lower extremity commonly affected	10-25%
Undifferentiated arthritis	Arthritis that does not satisfy inclusion criteria for any subtype, or meets the criteria for more than one	11-25%

1.1.2 Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is an autoimmune disease of the digestive system with an unknown aetiology. Although this inflammatory condition of the colon and small intestine does not lead to mortality, symptoms may flare and remit over time. IBD is classified into three types: Crohn's disease, ulcerative colitis, and indeterminate colitis, each with its specific characteristics as listed in Table 2. Crohn's disease can affect any part of the gastrointestinal system, from mouth to anus, and is characterized by

inflammation in the lining of the digestive tract which often spreads to deeper tissues. Ulcerative colitis only affects the colon and is characterized by inflammation of the innermost lining of the colon and rectum. The prevalence of pediatric IBD is 3 in 1000 in North America with Crohn's disease as the most common type in children, making the prevalence slightly higher than JIA (Shephard, 2016). What is more concerning is the incidence for IBD has significantly increased since the 20th century (Molodecky et al., 2012), and is most frequent in the Western world, ranging from 10 to 30 per 100,000 children (Ye et al., 2015). Due to shifts in lifestyle factors, this condition is becoming a growing problem in the Western world (Ye et al., 2015). These findings indicate that a growing number of individuals may become affected with symptoms such as diarrhea, fever, fatigue, cramping, and blood in stool. Additionally, these children may experience a reduced appetite and impaired nutrient absorption, which may lead to unintended weight loss (Stanisic & Quigley, 2014). During a sensitive period, such as the pediatric years, these devastating symptoms can be detrimental to proper growth into adulthood.

Table 2: Clinical presentations of Crohn's disease, ulcerative colitis, and indeterminate colitis. Frequencies are a percentage of all IBD cases (Winter et al., 2015; Bequet et al., 2016; Vernier-Massouille et al., 2008).

IBD Subtype	Feature	Frequency
Crohn's Disease (CD)	Inflammation anywhere from mouth to anus, rectal sparing; ulcers, abscess, weight loss/growth failure	59 – 73%
Ulcerative Colitis (UC)	Continuous inflammation in the innermost layer of the colon which spreads proximally; diarrhea, bleeding and pain	24 – 32%
Indeterminate Colitis (IC)	Colonic disease that cannot be classified as either Crohn's or UC	3 – 13%

1.1.3 Why Study JIA and IBD Together?

Evident from the incidence and prevalence rates, JIA and IBD are both common chronic conditions and with incident rates even growing in the case of IBD. The pathology for these conditions is still poorly understood but it may possibly be related to genetic and environmental factors (Ye et al., 2015; Eisenstein & Berkun, 2014), making prevention and cures likely unfeasible. While these conditions rarely lead to mortality on their own, they are very unpredictable in terms of symptoms, disrupting the routine for activities of daily living and impacting overall quality of life for these children. Furthermore, the inflammatory processes involved in the pathophysiology of these conditions place children at an increased risk of secondary health complications, including cardiovascular disease which is a major cause of premature mortality in these populations (Kavey et al., 2007; van den Hoek et al., 2017; Bartels et al., 2014). Although the underlying inflammation occurs in different parts of the body, there are many parallels in terms of treatment. Pharmaceutical treatment often involves use of a combination of non-steroidal anti-inflammatory drugs (NSAIDs), immunomodulators, biologics, corticosteroids, and amino salicylates. While treatment aims to start at as low a dosage as possible to prevent side effects, sometimes this is not enough. Some unwanted side effects from stronger treatments such as corticosteroids, biologics, and immunomodulators can include high blood pressure, osteoporosis, and growth suppression which may or may not be irreversible (Ruth and Passo, 2011; Blazina et al., 2016). Even drugs that are used to maintain remission produce side effects such as headaches, nausea, and fatigue (Pithadia and Jain, 2011). In practice, patients use a

combination of drugs to manage symptoms. This can have negative implications for their growth and development.

1.2 Physical Activity, Fitness and Health

Physical activity (PA) has been recognized as one of the most important therapeutic interventions for several diseases, particularly in those where the etiology is linked to metabolic or cardiovascular dysfunction (Franco et al., 2005; Henriksen, 2002). There is accumulating evidence of the significant benefits of PA and fitness on physical, mental, and biological health (Bilski et al., 2014). However, despite these benefits, children with chronic conditions may avoid PA for fear of exacerbating symptoms of pain, fatigue, or triggering a flare-up.

The terms physical activity, exercise, and physical fitness are often used interchangeably, but these terms are not synonymous. Exercise refers to a planned, structured, repetitive, and purposeful movement in which the maintenance or improvement of one or more components of fitness is the objective. Physical activity is defined simply as any bodily movement produced by skeletal muscle that results in energy expenditure (Caspersen, Powell, & Christenson, 1985). While physical fitness is defined as a set of attributes that people possess or achieve relating to the ability to perform physical activity (Caspersen, Powell, & Christenson, 1985). As such, fitness is comprised of physiologic measures such as muscular strength and cardiorespiratory capacity.

1.2.1 Physical Activity, Fitness and Health in Healthy Children

1.2.1.1 Physical Activity and Health in Healthy Children

Habitual PA and fitness are both well-established as independent predictors of health, in both children and adults (Hills, 2015). PA is essential for children throughout growth and maturation, improving not only physiological but psychological health as well. Guidelines published by the World Health Organization and several countries (Tremblay et al., 2011; WHO, 2011) recommend that children accumulate a minimum of 60 minutes of MVPA per day, as well as muscle and bone strengthening activities, at least three times a week. However, current statistics indicate only 33% of children meet this recommendation and that MVPA levels off as children get older (Colley et al., 2017). This is concerning as there is strong evidence, based on large-scale epidemiological studies, that a dose response relationship exists between engagement in physical activity and a decreased risk for cardiovascular disease (CVD) (Manson et al., 2002; Rockhill et al., 2001; Yu et al., 2003).

1.2.1.1.1 Measuring Physical Activity in Children

Measuring PA is difficult as there is no established gold standard method for assessing PA. Subjective methods such as questionnaires are often used due to ease of administration, particularly for large scale studies. The Physical Activity Questionnaire for Children (PAQ-C) has been widely used to assess PA in healthy school populations. This questionnaire was found to have high reliability but questionable validity for assessing total PA and MVPA in children (Benitez-Porres et al., 2016). When subjectively assessing PA in children, accuracy, recall, social desirability, and deliberate misrepresentation biases may be present (Metcalf et al., 2018). Therefore, physiological

sensor measures such as step counting or accelerometry have become increasingly popular in estimating PA. Although objective methods help to eliminate methodological bias, they are unable to provide information with regards to the type of PA. Despite a lack of consensus, ongoing development and application of accelerometers have provided significant advances in understanding PA in children and youth (Armstrong, 2013).

1.2.1.2 Aerobic Fitness and Health in Healthy Children

Aerobic fitness (i.e., cardiorespiratory fitness) is often used as an indicator for athletic performance, particularly in adults. In children, it is used more often as a proxy for different health outcomes. High cardiorespiratory fitness has been linked to lower body mass index (BMI), blood pressure, cholesterol, and other risk factors for cardiovascular disease in both adolescents and adults (Carnethon et al., 2003). In Canada., children are considered to be adequately fit, with an average cardiorespiratory fitness of 48.5 ml/kg/min, with girls being significantly less fit compared to boys, and fitness decreasing with age (Colley et al., 2019).

1.2.1.2.1 Measuring Aerobic Fitness in Children

Aerobic fitness is measured by obtaining maximal oxygen consumption (VO_2 max) and is the gold standard indicator of aerobic fitness (Shephard et al., 1958). Maximal oxygen consumption (VO_2 max) is measured during a graded maximal exercise test to volitional exhaustion on a bike or treadmill (Shephard et al., 1978). In adults, the termination criteria for the test include 1) a heart rate (HR) >200 bpm, 2) respiratory exchange ratio (RER) >1.0, and 3) a plateau in oxygen uptake. In children, this plateau may not always be present despite maximal effort, therefore, its often

referred to as VO_2 peak. Pediatric termination criteria include 1) a HR > 195 bpm, 2) RER > 1.0, and 3) an inability to maintain the prescribed pedalling cadence despite strong verbal encouragement (Takken et al., 2017).

1.2.1.3 Muscular Fitness and Health in Healthy Children

Muscle strength is often overlooked in research but is an important component of health and physical fitness. Muscle strength plays a role in the performance of many activities of daily living and is known to be an important predictor of physical function (Hislop, Avers, & Brown, 2014). In addition, muscle weakness is related to disability and is therefore an important outcome with regards to general health (Oliveira et al., 2017). Studies have reported that progressive moderate intensity and high-volume resistance training increased lean body mass in adolescents, paralleled by increases in muscular strength (Shaibi et al., 2006; Lee et al., 2012). Grip strength is a well-established independent predictor of all-cause mortality and CVD risk in adults (Rantanen et al., 2014; Lopez-Jaramillo et al., 2014). While the literature has mainly focused on aerobic fitness, research has shown that strength training can enhance efficacy and even promote exercise adherence as gains in strength can occur more rapidly than with aerobic training (Schranz, Tomkinson & Olds, 2013).

1.2.1.3.1 Measuring Muscle Strength in Children

In many research practices, common equipment/methods that provide quantitative measurements of strength, such as isokinetic and portable dynamometers, have been shown to be valid and reliable in children (Fagher, Fritzson, & Drake, 2016; Stark et al., 2011). Dynamometers are devices or apparatus that are used to measure power output or force. Knee extensors and flexors are commonly measured as the gold

standard of muscle strength because they have a key role in many functional and daily activities (Stark et al., 2011). If the equipment is not available, methods such as a strength and fitness battery are used to assess muscle strength in children. For example, a movement battery including handgrip test, push-ups, sit and reach, partial curl-ups, and vertical jump are validated for use (Alberga et al., 2017). Furthermore, there has been a larger focus on upper body strength as opposed to leg strength leading to a gap in the literature (Leong & Teo, 2015; Escobar et al., 2017).

1.2.2 Physical Activity, Fitness and Health in Children with JIA or IBD

Alarmingly, cross-sectional research has shown that children with JIA and IBD have decreased levels of physical activity, reduced muscle strength, and impaired aerobic fitness compared to healthy controls.

1.2.2.1 Physical Activity and Health in Children with JIA or IBD

There is a consensus from cross-sectional research, that children with JIA and IBD have lower levels of physical activity compared to their healthy peers (Henderson et al., 1995; Greenley et al., 2018). Children and adolescents with JIA also spend less time engaged in MVPA and do not meet the current daily guideline of 60 minutes of daily MVPA (Henderson et al., 1995), as recommended by the Canadian Society for Exercise Physiology (CSEP). These guidelines are important for health-related outcomes and optimal health (Bos et al., 2016), which are all the more important in children who have a chronic condition. Some health care providers remain concerned about PA and do not recommend sports for children when there is joint damage or inflammation (Takken et al., 2008). This has shown to be unfounded as research shows that exercise does not exacerbate arthritis (Maggio et al., 2010; Houghton, 2012). Indeed, a recent review

examining PA levels in children with JIA or IBD identified decreased physical activity and increased sedentary time, as factors that may exacerbate symptoms of health conditions (Bourdier et al., 2019).

Both subjective and objective methods of measurement have shown that children with JIA and IBD spend less time doing PA, regardless of its intensity (low, moderate, or vigorous). A decrease in MVPA levels (Cavallo et al., 2015) and increased time spent being sedentary has also been noted in children with JIA. There is a staggering assertion that only 23% of the pediatric population with a chronic condition meet the current PA recommendations compared to 66% of healthy children in the Netherlands (Lelieveld et al., 2008). Updated PA statistics in Canada estimate that only 33% of healthy children engage in MVPA (Colley et al., 2017). In 2012, Werkstetter and colleagues found that MVPA and TPA was even lower than healthy controls in children with IBD (Werkstetter et al., 2012). However, more recent research using objective tools to measure physical activity in children with JIA or IBD have not been published.

1.2.2.2 Aerobic Fitness in Children with JIA or IBD

Low aerobic fitness has been linked to an increased risk of developing secondary chronic conditions such as cardiovascular diseases, cancer, hypertension, as well as an increased risk of mortality in adults (Byberg et al., 2009). A review paper in 2002 showed that overall aerobic fitness as measured by VO_2 peak, measured over 6 research papers based on the standardized mean difference, is 21.8% lower in children with JIA than healthy children (Takken, Hemel, & Helders, 2002). Again, there is scant evidence for children with IBD, however, there is evidence showing children with IBD

have a lower VO_2 peak (75% of predicted) compared to reference values (Ploeger et al., 2011).

1.2.2.3 Muscle Strength in Children with JIA or IBD

Musculoskeletal fitness is positively associated with independent living and quality of life (Werkstetter et al., 2012). However, there is a paucity of research when it comes to muscle strength and musculoskeletal health, especially in children with JIA or IBD. The scarce amount of evidence that exists for children with JIA and IBD point to reduced muscle strength compared to healthy controls (Werkstetter et al., 2012; van Langenberg et al., 2014; Henderson et al., 1995; Bos et al., 2016). In particular, handgrip strength was significantly lower compared to healthy controls in both JIA and IBD (Rashed et al., 2019; Werkstetter et al., 1999). With regards to the lower limb, isometric maximal strength of the knee was assessed using a dynamometer chair by Saarinen et al., (2008). They found significantly lower muscle strength in the knee extensors of children with inactive JIA. However, after a 12-week home-based training program, involving free weights and rope skipping, an improvement in knee extensor strength was shown and maintained at the 6-month follow-up. This illustrates the positive utility of strength training within this population (Sandstedt et al., 2013).

1.3 How can Disease Activity Affect Physical Fitness and Physical Activity?

Disease activity and symptoms related to active disease, commonly referred to as sickness symptoms in the literature, are often suggested to be the main deterrents for physical activity, in turn leading to lower fitness levels (Bourdier et al., 2017). Both JIA and IBD are characterized by chronic inflammation of the body which can lead to

similar systemic symptoms. Sickness behaviours are a cluster of disabling symptoms that include fatigue, pain, and disturbed sleep (Cavallo et al., 2015).

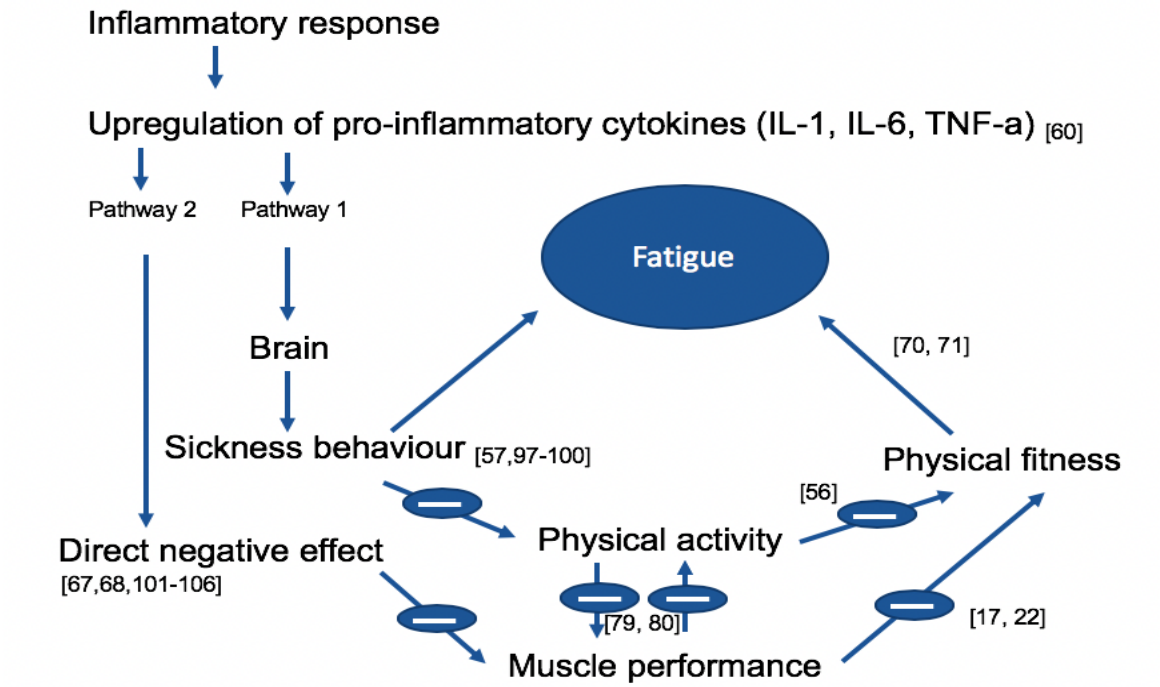

Figure 1: Conceptual model of action of pro-inflammatory cytokines and its impact on muscle strength, fitness, and physical activity, and their influence on feelings of fatigue. Taken from Vogelaar et al. (2015).

Figure 1 illustrates the conceptual model of action for inflammatory cytokines from disease activity, that lead to resultant sickness behaviours, including but not limited to fever, pain, and most notably, fatigue. These symptoms then lead to decreased physical activity and muscle performance, thereby decreasing physical fitness. This provides insights into a negative feedback loop created for the relationship between physical activity, fitness, and disease activity as these disease symptoms are often cited as barriers to being physically active and fit (Tew, Jones & Mikocka-Walus, 2016; Sharif et al., 2018). Indeed, children with chronic conditions often lead inactive lifestyles leading to deconditioning and functional deterioration, which again promotes an inactive

lifestyle. Functionally, this can lead to different impairments that can negatively impact the child during development, possibly leading to negative future health outcomes.

1.3.1 Disease Activity and Physical Activity in JIA and IBD

There is conflicting literature on physical activity and the effect of disease activity in children with JIA and IBD. Bohr et al. (2015), found that children with active disease had lower levels of PA than children in remission, suggesting that disease activity was the main deterrent for PA in these children. However, Gueddari et al. (2014) found that in children with JIA, disease activity, as measured by the Juvenile Arthritis Disease Activity Score (JADAS), was not related to physical activity (Greenley et al., 2018). JADAS combines physician and patient global assessments, joint counts, and erythrocyte sedimentation rate (ESR) in the blood, to create a disease activity score. This may suggest that control of disease activity is not sufficient to achieve recommended levels of physical activity. However, in many of these studies, physical activity was measured subjectively using activity diaries. Accelerometry is an objective method that is often used to more accurately measure PA. In a study by Nogaard et al. (2016), a negative correlation was found between accelerometer measurements of minutes of physical activity and JADAS values even when the participants had good disease control. Similar results were seen in children with IBD. Greenley et al. (2018) found that disease activity, as measured by the Manitoba IBD Index (MIBDI), contributed to decreased levels of physical activity, as measured through sports participation. The MIBDI is a single-item, self-report measure of disease activity over the span of 6 months. It is scored by a range of 1 (disease active every day) to 6 (in disease remission, absence of symptoms), and has been validated with other disease activity

measures of IBD (Greenley et al., 2018). These results support previous research that found physical activity, as measured with accelerometry, to be negatively associated with inflammatory indices of disease activity (CRP, ESR, leukocyte, hemoglobin, and thrombocyte count) (Mahlmann et al., 2017).

1.3.2 Disease Activity and Aerobic Fitness in JIA and IBD

A VO_2 max was used to test aerobic fitness in 31 children with JIA in a study by Maggio et al. (2010). Children and adolescents with JIA had a reduced aerobic fitness when compared to age-, weight-, and sex-matched healthy controls. Fitness levels were also found to be inversely correlated to disease activity and articular limitation ($p = 0.006$ and $p = 0.013$, respectively). This supported research that was done by Malleson et al. (1996 who found VO_2 peak to be negatively associated with disease activity, as measured by a physician global assessment. However, having also measured psychosocial factors, they suggested that these may be more important determinants of fitness than disease activity (Malleson et al., 1996).

There is a paucity of research that exists on aerobic fitness in relation to disease activity in children with IBD. However, existing research by Ploeger et al. (2011) reported that children with Crohn's disease and ulcerative colitis had 75% predicted aerobic fitness when compared to reference values of healthy children. This decrease was not found to be related to disease activity as measured by the Pediatric Crohn's Disease Activity (PCDAI) and Pediatric Ulcerative Colitis Disease Activity Index (PUCDAI). A possible explanation for the lack of relationship is that these measurements quantify disease activity as presented by common symptoms of IBD.

However, this does not account for the reduction in fitness that may exist during remission.

These findings give insight into the multifactorial variables that may be a barrier to fitness and physical activity for children with a chronic condition, and thereby, prompting a better method to quantify disease activity that may include patient self-report.

1.3.3 Disease Activity and Muscle Strength in JIA and IBD

Muscle weakness may limit participation in activities of daily living, including physical activity. Particularly, this is of concern in JIA as muscle weakness and atrophy persists around the active joint even into remission (Werkstetter et al., 2012). Lindehammar and Backman (1995) found reduced isometric knee extensor strength in 20 children with active arthritis. Values as low as 45-65% of the expected value in healthy children were reported in muscles around the actively inflamed joint. Strength in muscle groups that were not proximal to the active joint was only slightly, but significantly decreased (80-90% of predicted), suggesting a systemic factor is contributing to the decreased strength, possibly implicating disease activity. Recently, Rashed et al. (2018), built on this and measured isometric arm strength using a handgrip dynamometer in relation to health and function, as reported by the child with JIA. Grip strength had a significant inverse correlation to JADAS ($r = -0.467$, $p = 0.025$) which supports work done by Wessel et al. in 1999. The correlation is negative as a lower number indicates better health. In children with IBD, Lee et al. (2018) assessed peak isometric torque of the leg using Biodex, which is an isokinetic dynamometer.

Lower muscle torque and lean muscle mass were independently associated with clinical disease activity ($p < 0.05$) as well as serum TNF-α levels ($p \leq 0.04$).

Low lean body mass is a characteristic of JIA and IBD, and is even seen in states of remission, however, it is not certain that this is related to loss of strength (Lindehammer & Backman, 1995). A lower lean body mass contributes to the fatigue that is experienced by these patients, a hallmark symptom affecting individuals with both JIA and IBD (Lindehammer & Backman, 1995; Henderson et al., 1995). It is thought to be due to a smaller amount of muscle mass being available to generate force for a given workload, causing the muscle to experience fatigue sooner (Lindehammer & Backman, 1995). Fatigue has not been measured objectively in children, but in adults, van Langenberg et al. (2014) found that patients with Crohn's showed greater fatigue over 30 successive isokinetic contractions of the quadriceps compared to healthy controls. Findings of muscle fatigue (-5.2 vs -1.3 Nm/min; $p<0.05$) were correlated with higher levels of IL-6, a marker of disease activity. This supports the idea that disease activity involving the release of pro-inflammatory cytokines can trigger sickness behaviours patients experience, such as fatigue.

1.4 Disease Activity with Physical Activity and Fitness

There is no doubt that disease activity in children with JIA or IBD may be detrimental to physical activity and fitness levels. This is alarming as there is an abundance of evidence that supports and encourages the use of PA and exercise in this population (Sharif et al., 2018; Sands, 2015; Hosick et al., 2013). Not to mention, inactivity, poor aerobic and musculoskeletal fitness are associated with poor health

outcomes, including an increased risk for secondary chronic conditions such as CVD and even some types of cancer (Warbuton, Nicol & Bredin, 20016; Houghton, 2012; Shephard, 2016). Although CVD and cancer appear to be conditions that plague adults, the precursors to these conditions begin in childhood. A healthy lifestyle, including PA and exercise are important for lowering the risk of developing these secondary conditions. Evidence has shown that PA and exercise can be a useful therapy for individuals with chronic conditions. Some of the benefits include improving immune function, reducing fatigue, and promoting muscle strength (Sharif et al., 2018). Individuals who engaged in frequent physical activity, defined as greater than 30 minutes of MVPA a day, had lower levels of systemic inflammation, as measured by CRP levels, after adjusting for a variety of other factors (Sands, 2015).

Children with high aerobic fitness are also said to have healthier profiles of TNF-a and IL-6, markers of inflammation and indicators for disease activity (Hosick et al., 2013). Not only does PA improve disease activity through mechanisms involving cardiorespiratory and muscular fitness, but PA has been linked to various improvements in function, body composition, bone health, as well as self-reported indicators of health such as health related quality of life and well-being, and the reduction of fatigue (Bilski et al., 2014; Pedersen & Saltin, 2006; Booth et al., 2000; Wen et al., 2011; Basu et al., 2016; Rochette et al., 2015).

1.5 Self-Reported Measures of Health and Well-being and Physical Activity and Fitness

The current literature has emphasized using physician and clinical biomarkers to assess disease activity. While it may seem intuitive that disease activity is a barrier to physical activity and fitness, surprisingly, even when in remission, patients can experience sickness behaviours, such as pain, disability, and/or fatigue. These symptoms, even in the absence of active clinical disease, pose significant barriers to being physically active, and as a result being less physically fit (Ambrust et al., 2016).

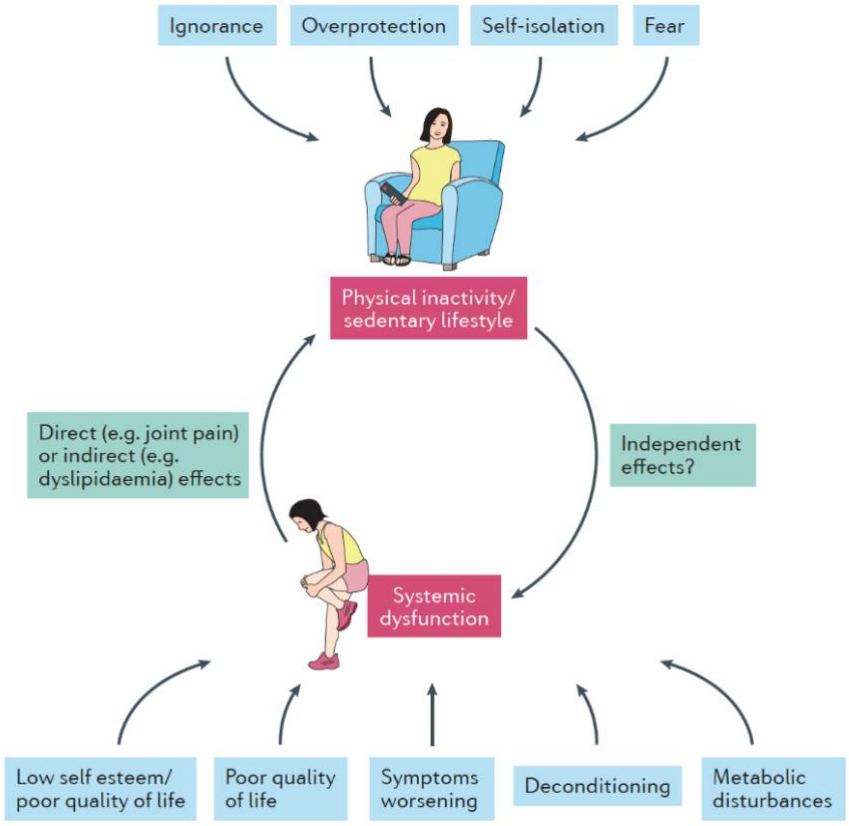

Figure 2: Multifactorial approach to the cycle of systemic dysfunction and physical inactivity. Taken from Gualano et al. (2017).

In a recent review, Gualano et al. (2017) provide an updated view on how a multitude of factors can lead to “systemic dysfunction” or sickness behaviours (Figure 2). This

shows that a variety of factors can contribute to how a child perceives their health and well-being, which can then directly or indirectly affect their physical activity, moving away from the idea of disease activity as characterized by proinflammatory markers or a physician assessment, as the sole contributor. Amongst these factors, are a variety of external psychosocial factors that can lead to systemic dysfunction (or sickness symptoms), contributing to a physically inactive lifestyle, which may independently contribute to systemic dysfunction and aggravation of symptoms, fueling a vicious cycle.

1.5.1 Self-Perceived Health and Well-being in Disease

Recent research has shown that there is a clear association between sickness behaviours and factors that influence perceived health and well-being (Ringold, Ward, & Wallace, 2013; Ambrust et al., 2016). Perceived health is an indicator of overall health status, usually rated on a scale from poor to excellent. This encompasses not only the absence of disease or injury, but includes overall physical, mental, and social well-being (Husu, Vaha-Ypya, & Vasankari, 2016). Whereas well-being is overall life satisfaction and rather than the absence of negative symptoms; referring to the presence of positive characteristics (happiness, satisfaction, optimal functioning) (Breslin et al., 2017).
This updated, multifactorial approach to sickness behaviours can help to explain the incongruency between patient perceived health and well-being and disease activity, as assessed by physicians. Teitelbaum et al. found a significant but weak correlation r = ((0.33, $p < 0.003$) – (r = 0.35, $p < 0.09$)) between symptom burden using a patient global assessment measure, and disease activity as measured by PCDAI and PUCDAI in children with IBD (Teitelbaum, Rajaraman, & Jaeger, 2013). Perceived health and

well-being may be a significant contributor to explain the discrepancy that exists with regards to the congruency between disease activity and patient symptom burden.

While there have been no studies on the influence of health perception and sickness behaviours in children, this relationship has been examined in adults. In a population with allergic asthma, poor self-rated health as measured by a single item questionnaire was significantly associated with higher levels of sickness behaviours and perennial immunoglobulin E (IgE), which are antibodies produced by the immune system in response to an allergen. This relationship was found to exist in both men and women, independent of age and BMI (Lodin et al., 2017). Additionally, illness perceptions and perceived health were found to be associated with physical symptoms such as fatigue and activity reduction in adults with chronic fatigue syndrome (Gucht et al., 2017). In a cohort of 72 530 Swedish men, after adjusting for standard risk factors, self-rated health was found to be an independent predictor of fatal or non-fatal myocardial infarctions among standard risk factors. All categories of self-rated health worse than “very good” had a dose response relationship risk for fatal of non-fatal myocardial infarction, even after adjusting for confounding variables (Waller et al., 2015). More research is needed on how these perceptions of health and well-being influence physical activity and fitness.

1.5.2 Self-Perceived Health and Well-being and Physical Activity and Fitness in Healthy Children

In healthy children, the relationship between perceived health and well-being with regards to fitness and physical activity, has also been explored. Husu et al. (2016), looked at objectively measured PA levels and associations with perceived health status.

They found that less sedentary behaviour and more time spent being physically active were associated with excellent perceived health in these children. Furthermore, healthy children who met the daily MVPA guidelines report a higher level of well-being, as measured by the KIDSCREEN-27 quality of life questionnaire, than children who did not meet physical activity recommendations (Breslin et al., 2017). A multinomial logistic analysis using data from 1665 participants showed that a significantly lower amount of time was spent in MVPA for participants who rated health as “alright” or “poor”. Participants with “poor” as opposed to “excellent” health spent a third of the time in MVPA (17 vs. 50 min) (von Rosen & Hagstromer, 2019). This finding was further confirmed from a large urban health study in Europe in 13 783 15-year-olds. After controlling for covariates including gender, BMI, and socioeconomic status, positive associations were shown between high levels of physical activity and good health. In this study, physical activity was measured using a physical activity questionnaire. Only children who achieved at least 60 minutes of PA a day over the past 7 days were considered “active”. The others were assigned to the inactive group. Health status was assessed using the commonly used the standard validated 5-point Likert rating scale (excellent, very good, good, fair or poor) (Granger et al., 2017). Whether or not the associations between perceived health and well-being are a barrier to PA should be investigated further, as there is strong evidence showing that regular PA in childhood and adolescence is beneficial for both physical health and on subjective health indicators.

Research examining the relationships between fitness and self-perceived health and well-being have been explored as well. In a recent study by Velez et al. in 2017,

7402 children between 9 and 12 years old completed a shuttle run test and were asked to rate their health. In both boys and girls, poor fitness increased the likelihood of poor self-rated health. Another study looking at the associations between self-rated health and cardiorespiratory fitness in adolescent girls found that girls who were classified as unfit were more likely to report negative self-rated health based on regression models (Mota et al., 2012). More research is needed to determine if these findings extrapolate to children with a chronic condition.

1.5.3 Self-Perceived Health and Physical Activity and Fitness in Children with a Chronic Condition

Studies have preliminarily explored more self-reported patient health measures in children with chronic conditions, understanding that sickness behaviours cannot be explained entirely by clinically measured disease activity (Mahlmann et al., 2017; Greenley et al., 2018). However, results appear to be conflicting. In children with type 1 diabetes, another chronic inflammatory condition, no significant associations were found between perceived well-being and physical activity through heart rate monitoring (Edmunds et al., 2007). The role of psychosocial factors has been examined in adults with IBD, but this area has scarcely been investigated in pediatric IBD (Mackner, Sisson, & Crandall, 2004). It was found that self-reported health measures such as fatigue, pain, depressive and anxiety symptoms were found to be negatively associated with physical activity, as measured through sports participation in children with IBD in bivariate analyses (Greenley et al., 2018). However, this relationship was not found in regression models with sports participation and psychosocial factors. At this point, it is evident that the relationship between perceived health, well-being and physical activity

and fitness is not fully understood in children with a chronic condition, and merits further investigation.

1.6 Summary and Rationale for Thesis

There is an alarming trend in which children with JIA and IBD have lower PA and fitness levels, compared to healthy controls, and this is partly due to disease activity. The classic view has been that inflammatory cytokines cause sickness behaviours however, these behaviours often persist even into remission prompting a more comprehensive measure of health in these children. Physical activity and fitness research in children with a chronic condition has primarily focused on the deconditioning aspect – a physically inactive lifestyle can lead to increased systemic dysfunction, which leads to lower perceptions of well-being and health. While this indicates a need for effective and timely interventions to increase physical activity and fitness levels in this population, little is known regarding the psychosocial factors that actually influence physical activity behaviours. Both perceived health and well-being have been scarcely examined in relation to fitness and physical activity in children with JIA and IBD, leaving a significant research gap in the literature. The proposed rationale for the relationship between these measures and physical activity and fitness is illustrated in Figure 3.

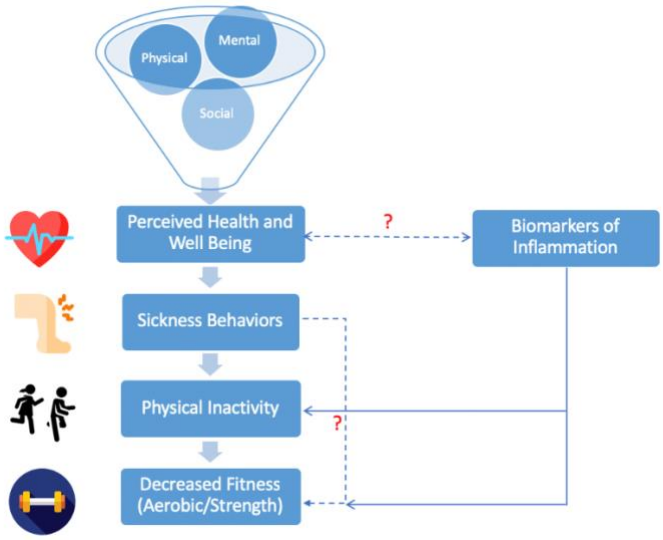

Figure 3: Proposed rationale for the multifactorial relationship leading to physical inactivity and decreased fitness levels in children with JIA or IBD. In the current literature, inflammatory markers are known to decrease physical activity and fitness. However, a variety of factors influence health and well-being which leads to the perception of sickness behaviours even when clinical markers of disease has cleared. It is proposed that these sickness behaviours create a cascade of deconditioning leading to physical inactivity and subsequently, decreased fitness, which furthers negative health outcomes. Dashed arrows indicate proposed relationships that have not been established in the current literature as of yet.

PA and fitness are positively associated with independent living, quality of life, and a reduced risk of a variety of secondary chronic conditions. This necessitates reliable and objective measurements of both PA and fitness in children to ascertain whether the child's perception of their health affects their fitness and PA levels. Before we are able to provide timely and effective interventions, it is necessary to understand what factors are preventing these children from being active initially. For these children, merely looking at clinical assessments of their disease activity is not enough to understand the multifactorial barriers that may contribute to their assessment of their perceived health and well-being. My research will be the first to examine the impact of perceived health and well-being on physical activity and fitness in these populations vulnerable to secondary health risks.

1.7 Objectives and Hypothesis

1.7.1 Research Questions

1) Is there a difference between perceived health, inflammatory blood markers, and physical activity and fitness in children with a chronic condition and healthy controls?
2) What is the relationship between self-perceived health and well-being and physical activity and fitness in children with a chronic condition?
3) What is the relationship between inflammatory disease markers, and self-perceived health and well-being in children with a chronic condition?

1.7.2 Objectives

1) a. To examine self-perceived health, moderate to vigorous physical activity, aerobic fitness, and muscle strength in children with JIA or IBD, compared to healthy controls.

b. To examine the relationship between inflammatory blood markers in children with JIA or IBD, compared to healthy controls.

2) To examine the relationship between self-perceived health and well-being and:

a. moderate-vigorous physical activity;

b. aerobic fitness;

c. muscle strength in children with JIA or IBD.

3) To examine the relationship between inflammatory blood markers and:

a. moderate-vigorous physical activity

b. aerobic fitness

c. muscle strength in children with JIA or IBD, and healthy controls.

1.7.3 Hypotheses

1) a. Children with JIA or IBD will have lower self-perceived health, moderate to vigorous physical activity, aerobic fitness, and muscle strength compared to healthy controls.

b. Children with JIA or IBD will have higher levels of inflammatory blood markers compared to healthy controls.

2) Children who perceived themselves to be healthier and well will engage in higher levels of moderate-vigorous physical activity, have greater aerobic fitness and muscle strength than those who perceive themselves to be less healthy and well.

3) Children with JIA or IBD who have higher levels of inflammatory blood markers will engage in less moderate-vigorous physical activity, be less aerobically fit and strong than children with lower levels of inflammatory blood marker activity.

CHAPTER 2: METHODS

2.1 CHAMPION Study Overview

My research is a sub-study of the ongoing **C**ardiovascular **H**ealth **A**ssess**M**ent in **P**ediatric chronic **I**nflammatory conditi**ON**s (CHAMPION) project. This sub-study followed children aged 7-17, with either juvenile idiopathic arthritis (JIA), or inflammatory bowel disease (IBD), and a healthy cohort (N = 30 per group). The Hamilton Health Sciences/ Faculty of Health Sciences Research Ethics Board provided ethical approval for the study.

2.2 Participants

2.2.1 Participants with a chronic inflammatory condition

Children between the ages of 7 and 17 years, with a confirmed, single diagnosis of JIA or IBD were recruited from clinics at the McMaster Children's Hospital. As diagnoses can change over time, only children who had a confirmed diagnosis for at least 1 year was approached. Additionally, participants were screened to have no new medications and no hospitalizations for 6 weeks and 3 months before the initial study visit, respectively. Patients with the systemic subtype JIA were excluded from the study, however patients with uveitis secondary to their JIA were included. Patients with IBD cannot be undifferentiated and must have been diagnosed with either Crohn's disease or ulcerative colitis.

2.2.2 Healthy control participants

Healthy controls include children aged 7 to 17 years without a medical condition. They also must not be participating in any medical program (e.g., weight management), and without a sibling with a medical condition, to avoid a possible influence of the home environment.

2.2.3 Recruitment strategy

Eligible participants with either JIA or IBD were identified at their regular clinic visits at McMaster Children's Hospital. A member of the clinic staff introduced the study to all eligible patients. If the child and their family were interested in learning more, a member of the study team discussed the study, answered any questions and obtained consent-to-contact for permission to follow up with the family outside of clinic. Participants for the healthy control group were recruited from the general community.

2.3 Study Protocol

Successfully recruited participants were asked to attend 2 study visits at the Child Health & Exercise Medicine Program. All attempts were made to schedule visits that coincided with their regularly scheduled clinic visits to minimize burden for the participants.

At visit one, participants were consented and completed medical questionnaires. They then underwent a basic anthropometric assessment, including the measurements of height, weight, and body composition. Next, we assessed the participant's fitness, starting with upper and lower body muscle strength followed by a recovery period and an aerobic fitness test. During the recovery period, participants filled out questionnaires about how they feel about physical activity, and how their condition may affect their physical activity. Before leaving the laboratory, an accelerometer to assess habitual physical activity was given to the participant and their parent/guardian along with detailed instructions on its use and an activity log book. At the second visit, participants arrived at the lab after an overnight fast, and a fasted blood sample was collected. They

also underwent ultrasound measurements of vascular structure and function and a motor skills assessment as part of the main CHAMPION study that was not used in this thesis. The total time commitment for each study visit was approximately 2.5 hours, including the few minutes per day needed to make entries into the accelerometer logbook.

2.4 Assessments

2.4.1 Descriptive measures

Basic anthropometric measurements were obtained, including height (cm), sitting height (cm), weight (kg). These were measured using a stadiometer and digital weight scale in duplicate for accuracy and in triplicate if values were not within 0.3 cm or 0.1 kg of each other. Height and weight were used to calculated BMI and BMI percentile. Sitting height was used to estimate years from peak height velocity, an indicator of maturation status (Mirwald et al., 2002). Body composition was also assessed, including percentage body fat and lean mass, measured by bioelectrical impedance analysis (InBody). A medical questionnaire was administered to determine medication use and duration of diagnosis for descriptive characteristics of the sample.

2.4.2 Self-Perceived Health and Well-being and Disease Activity

2.4.2.1 Self-Perceived Health

The KIDSCREEN-27 is a questionnaire measuring health related quality of life, with a section on physical health. Participants were asked “in general, how would you say your health is?” on a scale from “poor” to “excellent”, as seen in Appendix E. This

translated to a 5-point scale for analysis. This questionnaire was completed at the first study visit.

2.4.2.2 Self-Perceived Well-being

As part of the Child Health Assessment Questionnaire (CHAQ) completed at the first visit, participants were asked to assess their global well-being on a 10cm visual analogue scale (Sontichai & Vilaiyuk, 2018). Participants were prompted with: "considering all the ways your disease affects you. Please rate how you are doing by placing a mark on the line below". Participants then placed a tick on a line that ranged from "doing very well" at 0 cm and "doing every poorly" at 10 cm, as seen in Appendix D. This provided the measure for the child's perception of their health (Patient Global Assessment) which was supplemented by clinical measures such as the biomarkers of inflammation in the blood.

2.4.2.3 Biomarkers of Inflammation in the Blood

Inflammatory markers implicated in disease activity (C-reactive protein, interleukin-6, and tumor necrosis alpha) (Sharif et al., 2018) were obtained from a fasted blood sample in EDTA-treated vacutainers. Within 30 minutes of collection, the samples were centrifuged, and plasma was stored in aliquots at -80 degrees Celsius until analysis. To minimize inter-assay variability, samples were analyzed in batches using high sensitivity enzyme-linked immunosorbent assay (ELISAs) purchased from R&D Systems. Samples were run in duplicate and re-run if the coefficient of variation (CV) of the plate, as calculated by $CV = \frac{average\ of\ duplicated\ sample}{standard\ deviation\ of\ duplicated\ sample} * 100\%$, was greater than 10%. The standard curve was generated using a 4-parameter logistic regression curve fit to determine inflammatory marker concentration based on optical density. A

composite score of inflammation was used for analyses. Composite scores for the inflammatory markers were calculated according to the following equation:

$$Composite\ Blood\ Score = \ average\ (Zscore_{CRP}, Zscore_{TNF-a}, Zscore_{IL-6})$$

Z-scores were calculated using the equation: $\frac{x - \bar{x}}{standard\ deviation}$.

2.4.3 Fitness

Participants underwent physical fitness assessments to examine their aerobic fitness and muscle strength.

2.4.3.1 Grip Strength of the Upper Limb

Handgrip strength was measured using a handheld dynamometer (Takei Scientific Instruments, Tokyo, Japan), an isometric measurement used to quantify forearm muscle strength. Participants were instructed to stand with their arms extended by their side, with feet shoulder width apart, take a deep breath and to squeeze the device with their maximum effort while exhaling, accompanied by strong verbal encouragement. Both the dominant and non-dominant hand were tested 3 times or until 3 values within 3 kg of each other, were obtained. Participants alternated hands after each trial to allow for a brief period of rest and recovery. The peak value for the dominant hand was reported as kg per kg body mass.

2.4.3.2 Isometric, Isokinetic Strength and Fatigue of the Dominant Lower Limb

Lower body strength was assessed on the dominant leg using an isokinetic, isometric, and fatigue protocol on an isokinetic dynamometer (Biodex). Participants were strapped to the device to minimize contributing forces that were not created by the knee extensor and flexor muscles. To ensure maximum effort was being exerted, strong verbal encouragement and visual feedback of torque on the computer screen was

provided. The isometric protocol consisted of a series of alternating between maximal knee flexions and extensions while the dominant leg was fixed at 90-degrees. Each contraction was held for 5 seconds, and this protocol was repeated 3 times. Each trial was averaged for a single isometric extension or flexion leg strength measure and expressed as Nm/kg. The isokinetic strength test was measured at three angular velocities: 60, 120, or 180 degrees/second. This measure was repeated three times, with a three-minute rest period between trials. Peak values for both the isometric protocol were expressed as Nm/kg. The protocol measuring muscle strength and fatigability consisted of 50 consecutive maximal knee flexion and extension on the dominant limb, at an angular velocity of 180 degrees/sec. Values were reported as a rate of fatigue for flexion and extension. This was calculated by taking the average of the peak and minimum 3 torque measurements for either flexion or extension and put into the equation: $rate\ of\ fatigue\ (\%) = \frac{mean\ peak - mean\ minimum}{mean\ peak} * 100.$

Composite measures for isometric and isokinetic strength variables, as well as a composite score for all strength measures expressed in both absolute terms (N*m) and when expressed relative to body mass were compiled. The composite scores for isometric strength variables were calculated according to the following equation:

$Isometric\ Composite\ Strength = average\ (Zscore_{grip\ strength}\ ,\ Zscore_{isometric\ flexion}\ ,\ Zscore_{isometric\ extension})$

The isokinetic composite score was calculated according to the following equation:

$Isokinetic\ Composite\ Strength =$

$average\ (Zscore_{peak\ strength\ at\ 60\ deg/sec}\ , Zscore_{peak\ strength\ at\ 120\ deg/sec}\ ,$

$Zscore_{peak\ strength\ at\ 180\ deg/sec})$

The total strength composite score was calculated according to the following equation:

$$Composite\ Strength\ Score = average(Zscore_{grip\ strength}, Zscore_{isometric\ flexion}, Zscore_{isometric\ extension}, Zscore_{peak\ strength\ at\ 60\ deg/sec}, Zscore_{peak\ strength\ at\ 120\ deg/sec}, Zscore_{peak\ strength\ at\ 180\ deg/sec})$$

2.4.3.3 Aerobic Fitness

Aerobic fitness was measured using a graded cardiopulmonary exercise test using the McMaster All-Out Progressive Cycling protocol on a cycle ergometer. Participants pedaled continuously at 60 to 80 rpm as the resistance increased in fixed intervals every 2 minutes. The test was constructed according to body height and weight, such that the total exercise time would range from 8 to 12 minutes for most children. Pediatric-specific end criteria were used which includes: a HR of ≥195 bpm, a respiratory exchange ratio (RER) ≥ 1.0, and an inability to maintain the prescribed pedaling cadence despite strong verbal encouragement. Measurements of O_2 and CO_2 were assessed breath by breath using a calibrated metabolic cart (Vmax29, SensorMedics, Yorba Linda, CA, USA) with appropriately sized pediatric face masks. Volume of inspired O_2 was calculated from these measures. The highest 20-second volume of O_2 was considered maximal oxygen uptake, or VO_{2peak} (ml/kg/min), normalized to body weight to account for the large variation in age and size of the participants. Relative VO_{2peak} (ml/kg/min) is commonly used in the literature looking at fitness in healthy children as well as children with a chronic condition. VO_{2peak}FFM (fat free mass) is occasionally used when looking at children with a chronic condition but was not found to be significantly different when compared to VO_2 (ml/kg/min) with regards to studying inflammation and exercise in youth (McMurray et al., 2003).

2.4.4 Physical activity (PA)

Accelerometry is an objective measure of PA, providing duration, intensity, and frequency of movement and is valid for use in children with a chronic condition (Stephens et al., 2016; Trost et al., 2000). The standard approach is to monitor PA over 7 consecutive days of a typical week. In children with JIA, 1-week assessment with an accelerometer is sufficient to measure all levels of PA reliably (Ambrust et al., 2017). We used the ActiGraph GT3X accelerometer, a lightweight (27g) device fastened to an elastic belt that measures acceleration in three planes (vertical, horizontal, and mediolateral axes), worn over the right hip. The participants were instructed to record the times the device was taken off and put back on in a logbook. They were also given instructions to only remove the device before sleep, or before any activities involving water such as swimming or taking a shower. Data was collected in 3-second sampling intervals allowing for accurate classification of movement behaviours in children (Evenson et al., 2008). Acceleration data was converted into activity counts that allow for analysis with cut points. The number of minutes per day spent in moderate to vigorous (Loprinzi, 2015), and total activity time were analysed.

Accelerometer data was manually inspected to ensure that the time recorded in the logbooks matched the accelerometer's measurements with ActiLife software. Any activity counts recorded during reported times of non-wear as indicated in the logbook (Appendix C), were removed. All remaining "zero" activity counts were treated as sedentary time. PA was defined using cut-points specific to children from Evenson et al. (2008). Evenson et al. (2008), validated accelerometers against expired gas measures from a portable metabolic system. Sedentary time was considered to be less than 5

activity counts per 3 seconds while LPA was defined as ≥ 5 activity counts per 3 seconds, up to 115, while MVPA was classified as anything greater than 115 counts per 3 seconds. These values were obtained by dividing the Evenson cut points expressed in 60 second epochs by 20 to account for the 3 second epochs used here. This is common practice in PA research to accommodate different epochs (Nilsson et al., 2002). To account for different accelerometer wear times between children, PA (TPA and MVPA) was reported in relative terms, as a % of wear time (average PA per day / wear time per day*100) and relative to the number of days the accelerometer was worn (total PA / days worn). Only participants who wore the accelerometer for at least 10 hours a day, for at least 3 days were included in analyses.

2.5 Objectives and Statistical Considerations

Statistical Analyses were carried out with SPSS Statistics 20 for Mac (SPSS Inc., Version 20.0, Chicago, IL). Prior to analysis, all data were checked for normality using a Shapiro-Wilk test and were visually inspected using histogram plots. This was first done separately for JIA, IBD, and control groups, and repeated for JIA and IBD combined together. All parametric data were presented as mean ± standard deviation. All non-parametric data were presented as median (interquartile range). Statistical significance was set at $p<0.05$.

2.5.1 Participant Characteristics

Participant demographics and characteristics were analyzed separately for each condition, JIA or IBD, healthy controls, as well as an overall average. Most variables were normally distributed apart from self-perceived health and well-being variables, and

CRP, IL-6, and TNF-a. Blood marker data was successfully transformed to be normally distributed with a logarithmic transformation for CRP and IL-6 and an inverse transformation for TNF-a variables. Measures of self-perceived health and well-being remained non-parametric even after applying inverse, logarithmic square, and square root transformations. Therefore, the independent samples Kruskal-Wallis test was conducted over a one-way ANOVA between each group: JIA, IBD, and healthy controls, for measures of self-perceived health and well-being. All other variables were analyzed using the one-way ANOVA between each group.

2.5.2 Objective 1 Analyses

The first objective of this thesis was to examine the difference between self-perceived health, moderate to vigorous physical activity, aerobic fitness, muscle strength, and inflammatory blood markers in children with JIA or IBD, compared to healthy controls. The non-parametric Mann-U Whitney tests were used over t-tests to assess self-perceived health and well-being to determine whether they were significantly between children with a condition and healthy controls. All other variables were compared for difference of means using independent samples t-tests between children with a condition and healthy controls.

2.5.3 Objective 2 Analyses

The second objective of this thesis aimed to determine the relationship between self-perceived well-being and health and various physical activity, and fitness variables in children with a chronic condition. Whether or not there is a significant difference between the variables between children with a chronic condition and healthy children was established in the first objective. Linear regression models were used between

each dependent variable (self-perceived well-being and health) and the independent variables of PA, fitness and inflammatory blood markers to model relationships. The literature does not suggest causational relationships between the dependent and independent variables therefore, age, sex, and body fat percentage were added into the models to control for these variables.

2.5.4 Objective 3 Analyses

The third objective aimed to determine the relationship between inflammatory blood markers and various physical activity and fitness variables. Again, linear regression models were used to map out the relationship, along with age, sex, body fat percentage, and condition as a control. Here, condition refers to whether the participant has JIA, IBD, or is a healthy control.

2.5.5 Exploratory Analyses

The exploratory portion of this thesis aimed to understand whether there was a relationship between objectively measured muscle fatiguability, and self-perceived health and well-being, as well as inflammatory blood markers. A linear regression model of the rate of fatigue was submitted to different measures of physical activity, fitness, and inflammatory blood markers.

CHAPTER 3: RESULTS

3.1 Participant Characteristics

Participant characteristics are presented below in Table 3. Data was available for a total of 58 participants, 24 with JIA, 19 with IBD, and 15 healthy controls. Height and weight data were available for all participants. Percentage body fat was not available for three participants (2 in JIA, 1 in IBD) as the machine was non-operational for a period of time, and one participant (IBD) was unwilling to take off their socks. Due to the large variation in ages for the participants, height, weight, and BMI percentiles were calculated based on data from CDC growth charts (Ogden et al., 2002). A one-way ANOVA revealed significant differences ($p < 0.05$) in characteristics between children with JIA and IBD for height, weight, and BMI percentile, as well as significant differences in percentage body fat between children with JIA, IBD, and healthy controls. Children with JIA were significantly different from children with IBD for height, weight, and BMI percentiles. However, Spearman correlations did not reveal any associations between these variables and the dependent variables, self-perceived health and well-being. On average, children with JIA had higher percent body fat compared to children with IBD or healthy controls. Spearman correlations revealed a correlation between body fat percentage and the perceived health ($r = -0.285$, $p = 0.037$) variable. As a result, body fat percentage was added into the regressions models to control for this effect. Medication data was available for 39 participants (missing 4 from JIA) from a medical questionnaire. All participants were on medication except for 6 participants (4 JIA and 2 IBD), with the distribution for the types of medications listed in table 3. A confirmed date of diagnosis was missing from 5 participants (4 JIA and 1 IBD). There were no significant differences in disease duration, in years, between children with JIA

or IBD, as calculated from the difference of the date of their first visit to the date the families received a confirmed diagnosis.

Table 3: Participant characteristics according to group, as well as an overall average. Expressed as mean±SD. Age: chronological (date of visit 1 – date of birth). Disease duration (date of visit 1 - date of confirmed diagnosis). Values are presented as mean±SD. P-values represent the results of a one-way ANOVA between the groups – JIA, IBD, and healthy controls. * Denotes significance at $p<0.05$.

Variable	JIA	IBD	Controls	Overall	F p-value
n	24 (15 girls)	19 (12 girls)	15 (5 girls)	58 (32 girls)	-
Age (years)	12.9±2.9	14.2±2.0	13.6±2.8	13.5±2.7	0.320
Height (cm)	155.9±13.7	157.8±13.2	163.4±18.7	158.4±15.0	0.312
Weight (kg)	53.7±17.4	48.8±13.3	56.4±18.2	52.8±16.4	0.380
BMI (kg/m$_2$)	21.6±4.6	19.2±3.0	20.5±3.0	20.5±3.8	0.129
Height %ile	68.0±24.6*	46.6±30.2*	67.2±26.1	60.8±28.3	0.025*
Weight %ile	72.7±23.5*	45.8±30.3*	66.8±25.7	62.4±28.6	0.005*
BMI %ile	69.7±27.2*	45.7±31.0*	61.7±24.4	59.8±29.3	0.024*
Body Fat %	27.7±9.1*	18.2±8.5*	15.2±9.4*	21.3±10.4	0.000*
Years from Peak Height Velocity	0.3±2.6	0.9±2.1	0.7±2.4	0.6±2.4	0.130
Disease Duration (yrs)	4.1±2.8	4.5±4.9	-	4.3±3.9	0.746
Medications	7 Biologics 6 NSAID 10 Immuno-modulator 0 5-ASA 4 None	9 Biologics 0 NSAID 6 Immuno-modulator 4 5-ASA 2 None	-	16 Biologics 6 NSAID 16 Immuno-modulator 4 5-ASA 6 None	

3.2 Self-Perceived Health and Well-being

Table 4 displays the self-perceived health and well-being results from each of the JIA, IBD, and healthy control groups, and an overall average score of all the groups combined. Valid self-perceived health scores were available for 55 of 58 participants, missing one from each group (JIA, IBD, and controls). Self-perceived well-being scores were only available for most of the participants with JIA or IBD, with 43 scores, missing 2 from the JIA group. Missing values for self-perceived health and well-being scores were imputed using the mean substitution method to maintain statistical power. An

independent samples Kruskal-Wallis test was conducted to determine if there were differences in self-perceived health scores between JIA (n = 24), IBD (n = 19), and healthy controls (n = 15) groups. Values are mean ranks unless otherwise stated. Distributions of self-perceived health ratings were not similar for all groups, as assessed by visual inspection of a boxplot. Distributions of self-perceived health were higher in children with JIA (31.04) and healthy controls (32.33) compared to children with IBD (24.32), but the differences were not statistically significant, χ_2 (3) = 1.973, p = 0.373. On the perceived health scale from 1 to 5, on average, participants rated their health to be 3.8±0.9, which is between "good" and "very good" health. Participants with JIA or IBD on average rated their well-being as 1.38±2.10, which indicates they were in generally closer to the side of "doing very well".

Table 4: Self-perceived health and well-being variables according to group, as well as an overall average. Values are median (IQR). P-values represent the results of an independent samples Kruskal-Wallis test between the groups – JIA, IBD, and healthy controls. * Denotes significance at p<0.05.

Variable	JIA (n=24)	IBD (n=19)	Controls (n=15)	Overall (n=58)	K-W p-value
Self-perceived health	4(1.25)	3(1)	4(0.1)	4(1)	0.373
	25% Excellent 42% Very good 33% Good 0% Fair 0% Poor	21% Excellent 26% Very good 37% Good 16% Fair 0% Poor	13% Excellent 67% Very good 20% Good 0% Fair 0% Poor	21% Excellent 43% Very good 31% Good 5% Fair 0% Poor	
	JIA (n=24)	**IBD (n=19)**	**Controls (n=0)**	**Overall (n=43)**	
Self-perceived well-being	0.2(1.4)	0.4(2.0)	----	0.4(1.4)	0.651

3.3 Physical Activity

Valid accelerometer data were available for 52 participants. 4 participants were not included in analyses because they did not come back for a second visit (2 JIA, 1 IBD, 1 control) and one (JIA) did not meet the criteria of wearing the accelerometer for at least 3 days for ≥10 hours. One healthy control participant wore their accelerometer into a pool leading to water damage and with the device to no longer functional. Of the valid data, participants wore the accelerometers on average for a total of 6.9±0.5 days. On average, participants engage in 3.1 hours of TPA per day, which included an average of 53.6±23.2 minutes of MVPA per day across the 3 groups. A one-way ANOVA revealed children with JIA engaged in a higher percentage of LPA on average ($F = 3.787$, $p = 0.029$) compared to the other groups but only when expressed as a percentage of wear time. Table 5 provides a summary of the physical activity results according to group. Overall, the general patterns of physical activity were the same whether examined as minutes per day or, as %WT. In addition, only intensities of MVPA and TPA were examined in relation to this thesis, as the aim was to investigate whether children with a chronic condition are adequately active, and if their perception of health has an impact on their activity level. The variables that were included in the analyses align with current physical activity recommendations for optimal health (Tremblay et al., 2011).

Table 5: Physical activity results according to intensity per group, as well as an overall average expressed as minutes per day and as a percentage of wear time. Values are mean±SD. P-values represent the results of a one-way ANOVA test between the groups – JIA, IBD, and healthy controls. * Denotes significance at $p<0.05$.

Variable	JIA (n=21)	IBD (n=18)	Controls (n=13)	Overall (n=52)	*F* *p*-value
Wear Time (min/day)	754.6±120.1	762.3±92.4	794.4±55.9	767.2±97.4	0.503

Met PA Guidelines (%)	33%	22%	54%	35%	0.358
LPA (min/d)	150.0±52.5	113.8±40.8	130.1±38.9	132.5±47.3	0.055
MVPA (min/d)	53.3±22.4	46.3±24.6	64.3±19.5	53.6±23.2	0.099
VPA (min/d)	20.9±10.9	21.2±16.2	30.4±15.1	23.4±14.3	0.124
TPA (min/d)	203.3±67.3	160.1±57.1	194.4±29.5	186.1±61.8	0.078
LPA (%WT)	19.9±43.7*	14.9±44.2*	16.4±69.5	17.3±48.6	0.029*
MVPA (%WT)	7.1±18.6	6.1±26.7	8.1±34.9	7.0±23.8	0.207
VPA (%WT)	2.8±9.1	2.8±17.6	3.8±26.9	3.0±14.7	0.512
TPA (%WT)	26.9±56.1	21.0±61.8	24.5±88.5	24.3±63.4	0.067

3.4 Fitness

Table 6 displays the aerobic fitness results of 54 participants, 49 participants for isometric leg strength, and 46 for isokinetic leg strength. All 58 participants completed the grip strength test. For aerobic fitness, two participants with JIA cited mechanical limitations and one of them did not complete the test for this reason. One IBD participant looked very pale towards the end of the test and as a result, the experimenters terminated the test early. One healthy control participant was too small for the bike used with the metabolic cart and only completed a max power test. For leg strength, there were instances when the Biodex could not be accessed leading to the missing values for 8 participants. One participant was too small for the Biodex and did not complete the leg strength testing portion. Three participants were pressed on time and only completed the isometric test portion of the leg strength protocol, explaining the missing data for isokinetic leg strength. On average, a one-way ANOVA test indicated that aerobic fitness was significantly higher in healthy controls at 48.4±6.62 ml/kg/min ($F = 5.508$, $p = 0.006$) compared to children with JIA or IBD. Absolute and relative max power output ($F = 4.008$ and 5.010, $p = 0.041$ and 0.015, respectively), were significantly higher in healthy controls. Isometric and isokinetic leg extension at all

angular velocities were significantly in healthy controls. This difference was even more pronounced when the variables were expressed relative to body mass where all the individual strength measures were higher in the healthy controls, as seen in table 6. When presented as a composite score, only isokinetic strength remained significantly higher in the healthy control group (F = 7.066, p = 002) compared to the JIA or IBD group. However, when expressed relative to body mass, composite isometric, isokinetic and strength scores were found to be significantly higher in healthy controls (F = 7.137 and F = 9.652 and F = 10.225, p = 0.002 and p = 0.000 and p = 0.000, respectively).

Table 6: Aerobic and muscle fitness results per group as well as an overall average. Values are mean±SD. P-values represent the results of a one-way ANOVA test between the groups – JIA, IBD, and healthy controls. * Denotes significance at p<0.05.

Variable	JIA (n = 23)	IBD (n = 17)	Controls (n = 14)	Overall (n = 54)	*F p*-value
VO_2peak (ml/kg/min)	40.4±6.4*	41.8±8.8*	48.4±6.6*	42.9±7.9	0.007*
VO_2peak (ml/kgFFM/min)	55.5±7.7	51.5±6.1	57.7±6.4	54.9±7.2	0.062
HRMax (bpm)	194.2±18.7	199.3±7.6	194.8±10.5	196.0±13.8	0.515
WMax (W)	136.3±43.2*	140.9±52.9	182.1±60.5*	150.2±54.1	0.024*
WMax (W/kg)	2.6±0.6*	2.9±0.7	3.3±0.7*	2.9±0.7	0.010*
WMax (w/kgFFM)	3.6±0.7	3.7±0.8	3.9±0.6	3.7±0.7	0.533
Variable	**JIA (n = 20)**	**IBD (n = 16)**	**Controls (n = 13)**	**Overall (n = 49)**	***F p*-value**
Grip Strength (kg) (n = 58)	21.1±6.3	22.5±7.8	29.4±11.6	23.7±8.9	0.055
Grip Strength (kg/kg) (n = 58)	0.4±0.1*	0.5±0.1	0.5±0.1*	0.5±0.1	0.016*
Isometric Flex (N*m)	58.7±20.8	57.4±18.5	83.2±41.8	64.8±29.0	0.076
Isometric Flex (N*m/kg)	1.1±0.2*	1.2±0.2	1.4±0.5*	1.2±0.4	0.014*
Isometric Ext (N*m)	133.2±53.5*	134.4±42.4*	184.0±76.5*	147.1±60.5	0.018*
Isometric Ext (N*m/kg)	2.4±0.6*	2.7±0.6	3.0±0.7*	2.8±0.7	0.030*
Variable	**JIA (n = 18)**	**IBD (n = 16)**	**Controls (n = 12)**	**Overall (n = 46)**	***F p*-value**
Peak Flex 60 deg/s (N*m)	56.0±25.5	53.8±19.22	81.4±33.2	61.8±27.9	0.132

Peak Flex 60 deg/s (N*m/kg)	1.0±0.3*	1.1±0.2	1.3±0.4*	1.1±0.3	0.010*
Peak Ext 60 deg/s (N*m)	97.5±43.8*	108.2±34.1	160.2±60.1*	117.6±51.7	0.012*
Peak Ext 60 deg/s (N*m/kg)	1.8±0.6*	2.2±0.4*	2.6±0.5*	2.1±0.6	0.000*
Peak Flex 120 deg/s (N*m)	46.3±20.4	47.2±16.6	73.2±31.2	53.6±25.0	0.090
Peak Flex 120 deg/s (N*m/kg)	0.8±0.2*	0.9±0.2	1.2±0.4*	1.0±0.3	0.004*
Peak Ext 120 deg/s (N*m)	82.7±36.7*	91.3±30.6	138.3±53.5*	100.2±45.4	0.010*
Peak Ext 120 deg/s (N*m/kg)	1.5±0.5*	1.8±0.4*	2.3±0.5*	1.8±0.5	0.002*
Peak Flex 180 deg/s (N*m)	41.2±2*	41.8±16.9	65.5±25.0*	47.8±22.8	0.020*
Peak Flex 180 deg/s (N*m/kg)	0.8±0.2*	0.8±0.3	1.1±0.3*	0.9±0.3	0.004*
Peak Ext 180 deg/s (N*m)	72.9±32.3*	76.0±25.4	118.7±51.3*	86.0±40.5	0.014*
Peak Ext 180 deg/s (N*m/kg)	1.3±0.4*	1.5±0.4	1.9±0.5*	1.5±0.5	0.002*
Rate of Fatigue Flex (%)	68.8±14.3*	56.5±13.8*	70.0±15.4*	65.0±15.4	0.022*
Rate of Fatigue Ext (%)	54.3±12.1	55.1±4.0	56.0±11.7	55.0±9.8	0.864
Variable	**JIA (n=24)**	**IBD (n=19)**	**Controls (n=15)**	**Overall (n = 58)**	***F p*-value**
Composite Score Isometric	-0.3±0.7	-0.2±0.8	0.5±1.2	-0.1±2.0	0.082
Relative Composite Isometric	-0.4±0.7*	0.06±0.6	0.5±1.0*	-0.02±0.9	0.002*
Composite Score Isokinetic	-0.3±0.8*	-0.2±0.6*	0.7±1.1*	0±0.9	0.002*
Relative Composite Isokinetic	-0.5±0.8*	-0.1±0.5*	0.6±0.8*	-0.09±0.8	0.000*
Strength Composite Score	-0.4±0.8	-0.4±0.7	0.4±1.3	-0.2±1.0	0.099
Relative Strength Composite Score	-0.5±0.7*	-0.01±0.6*	0.5±0.8*	-0.09±0.8	0.000*

3.5 Inflammatory Blood Markers

Table 7 displays the results for the concentrations of CRP, IL-6, and TNF-a for 51 participants. Blood samples were not available for 1 JIA and 2 IBD participant due to difficulties obtaining a blood sample and 4 (2 JIA, 1 IBD, 2 healthy control) participants did not return for a second visit. The intra-assay CVs for the plates were 4.15%, 3.17%, and 1.66% for CRP, TNF-a, and IL-6, respectively. Individual markers were made into an overall inflammatory marker composite score for analyses. CRP levels are considered “normal” when they are below 3 mg/L. CRP levels higher than 3 mg/L have been seen to be independently associated with an increased risk in coronary heart disease (Yousuf et al., 2013). Normal circulating values of IL-6 are in the 1 pg/mL range (D’Auria et al., 1997). For TNF-a, there is less data regarding healthy ranges, but an upper reference limit of 2.53 pg/mL has been established (Todd et al., 2013). All inflammatory markers were under these thresholds with CRP averaging 1.2±2.9 mg/L, 1.3±1.5 pg/ml for IL-6, and 2.4±3.3 pg/mL for TNF-a. A Kruskal-Wallis test was conducted to determine if there were differences in inflammatory blood marker concentration for children with JIA, IBD, and healthy controls. Distribution of TNF-a was not similar for all groups, as assessed by visual inspection of a boxplot. Median TNF-a scores were significantly different between JIA, IBD, and healthy control groups, χ^2 (3) = 9.952, p = 0.007). Subsequently, pairwise comparisons were performed using Dunn’s (1964) procedure with a Bonferroni correction for multiple comparisons. This post hoc analysis revealed significant differences in TNF-a scores between JIA (mean rank =

22.05) and IBD (mean rank = 35.24, p = 0.020) groups as well as IBD and healthy control (mean rank = 20.31, p = 0.019) groups.

Table 7: ELISA results for inflammatory blood markers per group, as well as an overall average. Values expressed as median (interquartile range). P-values represent the results of a Kruskal-Wallis test between the groups – JIA, IBD, and healthy controls. * Denotes significance at p<0.05.

Variable	JIA (n = 21)	IBD (n = 17)	Controls (n = 13)	Overall (n = 51)	*K-W p*-value
CRP (mg/L)	0.3(0.5)	0.3(1.0)	0.3(0.8)	0.3(0.9)	0.943
TNF-a (pg/mL)	1.0(0.5)*	1.6(5.1)*	1.0(0.5)*	1.1(0.8)	0.007*
IL-6 (pg/ml)	1.3(1.0)	1.2(1.3)	0.7(0.6)	1.0(0.9)	0.094
Composite Blood Score	-0.3(0.5)	0.07(1.2)*	-0.3(0.2)*	-0.2(0.6)	0.005*

3.6 Objective 1 Results

The first objective was to examine the difference between self-perceived health, PA, aerobic fitness, muscle strength, and inflammatory blood markers in children with JIA or IBD, in comparison to healthy controls. Children with JIA or IBD were grouped together into a “disease” group and variables were compared to healthy controls. Independent sample t-tests showed that those with JIA or IBD spent a significantly lower amount of time in moderate-vigorous physical activity (t = -1.977, p = 0.040) compared to healthy controls, as pictured in figure 4. In terms of fitness, relative VO2 peak (t = -3.285, p = 0.002), Watts max (t = -2.841, p = 0.006), and Watts max/kg (t = -2.688, p = 0.010) were significantly lower in JIA or IBD groups, compared to healthy controls. All composite strength measures expressed in absolute terms or relatively, including isometric (t = -2.867, p = 0.006), isokinetic (t = -3.791, p = 0.000), total composite strength (t = -2.890, p = 0.005) and relative isometric (t = -3.118, p = 0.003), isokinetic (t = -3.925, p = 0.000), total composite strength measures (t = -3.659, p = 0.001) were significantly lower between children with a condition, compared to healthy controls. With regards to inflammatory blood markers, only IL-6 (t = 2.105, p = 0.040)

and a composite inflammatory marker score (t = 2.395, p = 0.021) were significantly different between the two groups. All other variables, including self-perceived health (U = 365, z = 0.793, p = 0.428), were not significantly different when submitted to Mann-Whitney U tests in children with a condition, compared to healthy children.

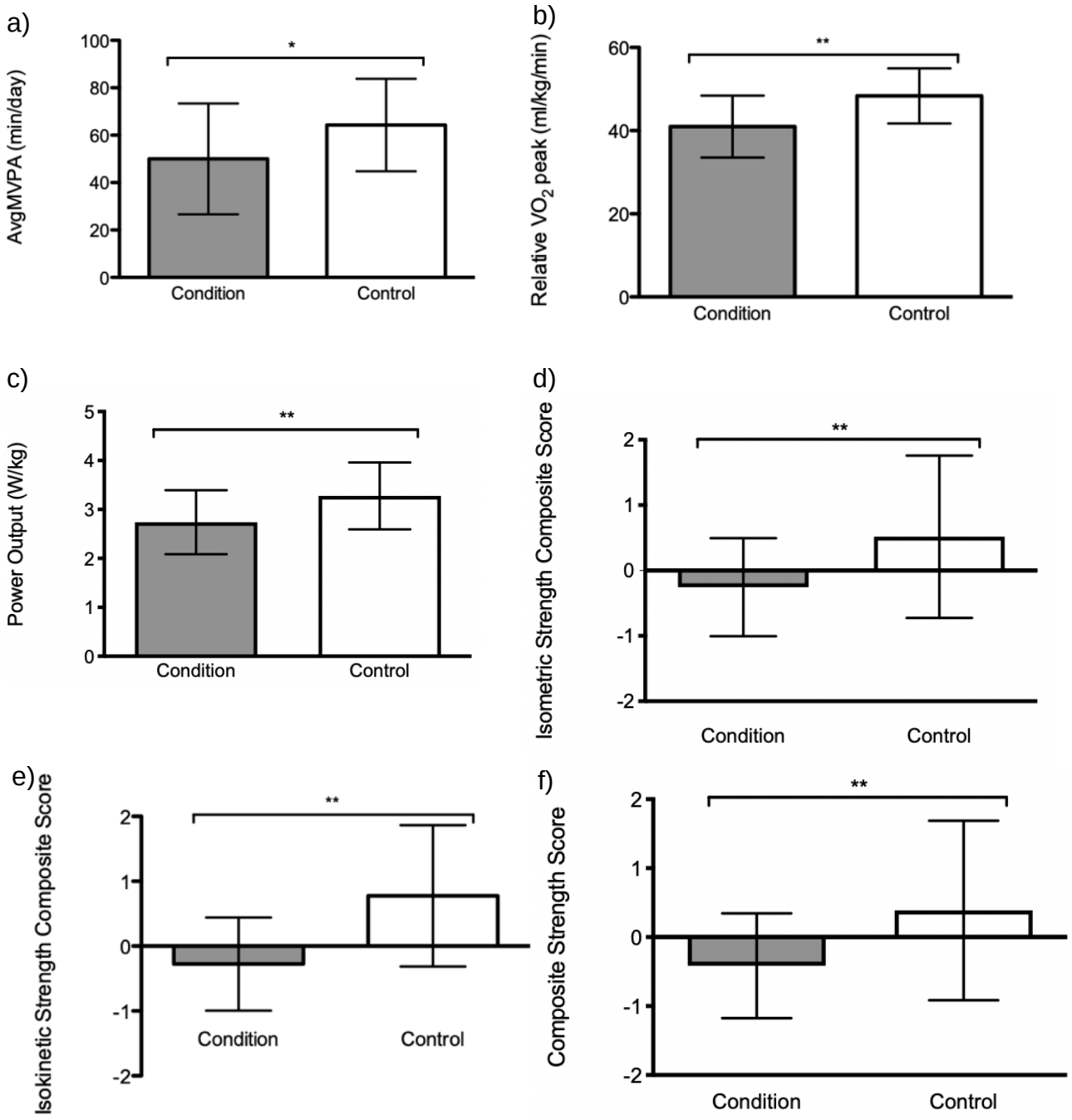

Figure 4: Physical activity and fitness results displayed by condition (JIA or IBD) and controls. a) average moderate-vigorous physical activity as expressed in minutes per day b) aerobic fitness as measured by VO_2 peak expressed in ml/kg/min c) power output expressed in W/kg d) composite score of all isometric strength measures e) composite score of all isokinetic strength measures f) composite score of all strength measures. Values are means ± SD. * Denotes significance at p<0.05. ** Denotes significance at p<0.01.

3.7 Objective 2 Results

The second objective was to examine the relationship between self-perceived health and well-being, and physical activity and fitness. This part of the analysis used a linear regression model to predict the relationship, displayed in table 8. A linear regression established that average MVPA per day could statistically significantly predict self-perceived health, $F(1,50) = 6.516$, $p = 0.014$ and MVPA accounted for 11.5% of the explained variability in self-perceived health. The regression equation was as follows: self-perceived health = 3.10 + 0.012*(average MVPA/day). This remained true when MVPA was expressed as a percentage of wear time, $F(1,50) = 7.249$, $p = 0.010$, where MVPA expressed as a percentage of wear time accounted for 12.7% of the explained variability in self-perceived health. The regression equation was as follows: self-perceived health = 3.047 + 0.101*(MVPA % WT). MVPA could no longer significantly predict self-perceived health with age, sex, and body fat percentage added into the model. Similarly, MVPA as a percentage of wear time could statistically significantly predict self-perceived well-being, $F(1,37) = 4.435$, $p = 0.042$, where MVPA % WT accounted for 10.7% of the explained variability in self-perceived well-being. The regression equation was as follows: self-perceived well-being = 2.656 – 0.209*(MVPA % WT). MVPA % WT could no longer significantly predict self-perceived well-being with age and sex added into the model.

Fitness measures could weakly predict self-perception measures. Watts max expressed relative to body weight was found to be the strongest predictor for self-perceived health, $F(1,53) = 5.148$, $p= 0.027$, where relative maximal power output

accounted for 8.9% of the variability seen in self-perceived health. However, this was no longer true when controls sex, age, and body fat percentage added into the predictive model. Fitness was a stronger predictor of self-perceived well-being, particularly relative VO_2 peak, $F(1,38) = 6.683$, $p = 0.014$, where relative VO_2 peak accounted for 15% of the variability with self-perceived well-being. The regression equation was as follows: self-perceived well-being = 5.205 – 0.098*(relative VO_2 peak). The model could no longer statistically significantly predict self-perceived well-being when age and sex were added into the models as controls. Composite measures of strength expressed absolutely or relative to body mass was not found to significantly predict self-perceived health or well-being.

Table 8: Summary of linear regression results for dependent variables self-perceived health and well-being and physical activity and fitness. * Denotes significance at p<0.05.

Model	Unstandardized coefficients		t	Sig.	95% Confidence Interval for B	
	B	Std. Error			Lower	Upper
Dependent var.: Self-Perceived Health						
Model	$R_2 = 0.115$		p = 0.014			
(Constant)	3.100	0.278	11.163	0.000	2.542	3.658
Avg MVPA	0.012	0.005	2.553	0.014*	0.003	0.022
Model	$R_2 = 0.127$		p = 0.010			
(Constant)	3.047	0.283	10.749	0.000	2.478	3.616
MVPA %WT	0.101	0.037	2.692	0.010*	0.026	0.176
Model	$R_2 = 0.089$		p = 0.027			
(Constant)	2.742	0.472	5.811	0.000	1.796	3.689
WattsMax/kg	0.361	0.159	2.269	0.027*	0.042	0.680
Model	$R_2 = 0.059$		p = 0.077			
(Constant)	2.653	0.636	4.173	0.000	1.377	3.928
VO_2 max (ml/kg/min)	0.026	0.015	1.803	0.077	-0.003	0.056
Model	$R_2 = 0.008$		p = 0.511			
(Constant)	3.793	0.112	33.814	0.000	3.568	4.018
Composite Strength	0.075	0.113	0.662	0.511	-0.151	0.300
Dependent var.: Self-Perceived Well-Being						
Model	$R_2 = 0.095$		p = 0.056			
(Constant)	2.558	0.719	3.556	0.001	1.101	4.016
Avg MVPA	-0.026	0.013	-1.975	0.056	-0.052	0.001
Model	$R_2 = 0.107$		p = 0.042*			
(Constant)	2.656	0.724	3.669	0.001	1.189	4.123
MVPA %WT	-0.209	0.099	-2.106	0.042*	-0.410	0.008

Model	R_2 = 0.087		p = 0.065			
(Constant)	3.526	1.254	2.812	0.008	0.988	6.064
WattsMax/kg	-0.848	0.446	-1.903	0.065	-1.749	0.054
Model	R_2 = 0.150		p = 0.014			
(Constant)	5.205	1.573	3.310	0.002	2,002	8.389
VO_2 max (ml/kg/min)	-0.098	0.038	-2.585	0.014*	-0.174	-0.021
Model	R_2 = 0.008		p = 0.569			
(Constant)	1.280	0.360	3.558	0.001	0.554	2.007
Composite Strength	-0.241	0.419	-0.575	0.569	-1.088	0.606

3.8 - Objective 3 Results

The third objective was to examine if PA, aerobic fitness, and muscle strength measures could be predictive of inflammatory blood marker concentrations. Physical activity, $F(1,47) = 0.278$, $p = 0.600$, and fitness variables, $F(1,48) = 3.437$, $p = 0.070$, were not found to be able to predict inflammatory blood marker concentrations, apart from a composite isometric strength score expressed relative to body mass, $F(1,49) = 4.447$, $p = 0.040$ where a composite isometric score accounted for 8.3% of the variability in a composite blood marker score. The predictive equation was as follows: composite blood score = 0.010 – 0.214*(relative composite isometric strength). With the controls age, sex, condition (JIA, IBD, or healthy control) added in as controls, 21.6% of the variability was accounted for however, this did not reach statistical significance.

Table 9: Summary of multivariate linear regression results for inflammatory markers and physical activity and fitness. * Denotes significance at p<0.05.

Model	**Unstandardized coefficients**		**t**	**Sig.**	**95% Confidence Interval for B**	
Dependent var.: IM	B	Std. Error			Lower	Upper
Model	R_2 = 0.006		p = 0.600			
(Constant)	0.128	0.243	0.527	0.601	-0.361	0.616
AvgMVPA	-0.002	0.004	-0.528	0.600	-0.011	0.006
Model	R_2 = 0.067		p = 0.070			
(Constant)	0.673	0.379	1.775	0.082	-0.089	1.436
WattsMax/kg	-0.236	0.128	-1.854	0.070	-0.493	0.020
Model	R_2 = 0.043		p = 0.148			
(Constant)	0.740	0.518	1.429	0.159	-0.301	1.781
VO2 Max (ml/kg/min)	-0.017	0.012	-1.471	0.148	-0.041	0.006

Model	R_2 = 0.083		p = 0.040*			
(Constant)	0.010	0.089	0.108	0.914	-0.168	0.188
Rel. Composite ISOM	-0.214	0.101	-2.109	0.040*	-0.418	-0.010
Model	R_2 = 0.025		p = 0.267			
(Constant)	-0.014	0.092	-0.152	0.880	-0.199	0.171
Composite Strength	-0.105	0.093	-1.124	0.267	-0.292	0.083

3.9 – Exploratory Analyses

The exploratory analysis section examined the relationship between objectively measured muscle rate of fatigue in comparison to self-perceived ratings of health and well-being, as well as inflammatory blood markers. The inflammatory marker TNF-a was able to statistically significantly predict the rate of fatigue for flexion, $F(1,41) = 9.253$, $p = 0.004$. TNF-a accounted for 18.4% of the variability with rate of fatigue for flexion. The predictive equation was as follows: rate of fatigue for flexion = 71.142 – 2.399*(TNF-a). TNF-a approached significance when predicting rate of fatigue for extension, $F(1,45) = 3.919$, $p = 0.54$, explaining 8% of the variability. The equation was as follows: rate of fatigue for extension = 54.414 – 1.498*(TNF-a).

CHAPTER 4: DISCUSSION

DISCUSSION

The disparity between the physical activity and fitness levels between children with a chronic condition relative to their healthy peers has been well-researched, focusing mainly on disease activity as an explanation. This thesis served to fill a significant research gap regarding the relationship between measures of physical activity, aerobic fitness, muscle strength and self-perceived health and well-being. Associations of perceived health and perceived well-being have been explored to a greater extent in healthy children, but much less is known about these associations in children with a chronic condition. Using self-perception measurement tools may be a helpful addition in both clinical settings and research setting providing a more thorough examination of overall health. Not only does it provide us with an idea of physical health and well-being, it also assesses psychological and social dimensions as well, which are known to impact a child's willingness to participate in physical activity, which can in turn impact fitness. The first step to filling this research gap was to determine if there were significant differences in physical activity and fitness levels between children with a chronic condition, and healthy controls. This helped us to confirmed that our sample is more fit compared to past literature. Next, the relationship between physical activity and self-perceived health and well-being were placed into linear regression models. This was repeated for the aerobic fitness and muscle strength measures. This was done in hopes to delineate the impact self-perceived health and well-being can have on these different measures. Lastly, the relationship between physical activity and fitness measures were modeled in relationship to inflammatory markers as these are part of the

current standard for diagnostics and follow-up for those with a chronic condition. In order to investigate these relationships, various regression models were explored.

4.1 Characteristics of Children with JIA or IBD, and Healthy Controls

The participants in this study ranged in age from 7-17 years, with the average age being 13.51±2.65 years, and was not significantly different between groups. Even with a wide age range, our sample was comparable to many other studies done in children with JIA or IBD (Velez et al., 2017, Greenley et al., 2018; Rashed et al., 2018). Although the healthy controls were in significantly higher height, weight and BMI percentiles, this did not impact any of the dependent variables. Spearman correlations revealed a significant relationship between body fat percentage, so this variable was included in regression models as a control. The regression models were not strengthened with the inclusion of age, sex, and body fat percentage as controls.

4.2 Self-Perceived Health and Well-being in Children with JIA or IBD

There were no significant differences between self-perceived health and well-being in our sample, with most children rating themselves around the “very good” to “excellent” range for health, and “doing very well” for well-being. This is contrary to the current study’s hypothesis and some of the studies on self-perceived/rated health or well-being in children. This may be explained by previous researchers being able to recruit more children who were doing “poorly” (Kwon et al., 2018; Granger et al., 2017). Additionally, this may be explained by the study’s inclusion criteria to screen for participants to have a confirmed diagnosis of JIA or IBD for at least a year. This may

have given our participants some time to adjust to their diagnosis and find mechanisms to cope with the changes and challenges due to their condition compared to those who would have been newly diagnosed.

4.3 Physical Activity in Children with JIA or IBD

Physical activity levels and trends were quite variable depending on the intensity. There were no significant differences between wear time for each of the groups. It was found that children with JIA were just as active as healthy controls, which is contrary to many other studies findings (Sherman et al., 2018; Gueddari et al., 2014). Indeed, children with JIA in our sample engaged in higher levels of TPA and LPA on average per day, compared to healthy controls. In line with previous literature, children with IBD engaged in lower levels of TPA, MVPA, and LPA, relative to healthy controls. Although these relationships were non-significant, these results approached significance. Furthermore, we found that children with JIA and IBD engage in lower levels of MVPA per day, with only the healthy controls meeting the daily recommendations of MVPA at 64.3±19.5 min/day, while children with JIA or IBD fell below that threshold at 53.3±22.4 min/day and 46.3±24.6 min/day, respectively.. Optimistically, 54% of healthy controls met the guidelines, compared to the provincial average which was found to be 33% in 2017, which is more representative of the children in our cohort with JIA or IBD, at 33% and 22% of them meeting guidelines, respectively. However, our findings were comparable to the sample by Maggio et al., in 2010, where they indicated that 38.1% of their cohort of children with JIA were meeting physical activity guidelines, and 60.4% of their healthy controls. It was promising to see that in our sample, children with JIA also

engaged in higher levels of TPA than healthy controls. Particularly, a large percentage of their time spent being active, was in LPA. Conversely, this resulted in less participation in VPA, relative to healthy controls. This is concerning as higher intensities of PA are most related to fitness (Dencker et al., 2006). An explanation for this is that children with JIA take part in lower intensities of PA out of fear of movement and exacerbation of pain (Bourdier et al., 2019). This prompts an important update in the thinking that children with JIA are inactive and potentially shift the focus to be placed on encouraging them to take part in more vigorous activities.

4.4 Fitness in Children with JIA or IBD

Participants performance on the aerobic and muscular fitness assessments are in line with the current literature that have demonstrated that children with a chronic condition are less fit than healthy controls. Indeed, in the assessment of aerobic fitness, children with JIA or IBD were significantly less fit compared to healthy controls at 48.4±6.6 ml/kg/min. Our sample of healthy controls were slightly more fit than healthy controls in a meta-analysis conducted by Takken et al., 2002, where their average VO2 peak over 5 studies was 41.8±2.5 ml/kg/min. This is similar to our cohort of children with JIA and IBD with a VO_2 peak value of 40.4±6.4 ml/kg/min and 41.9±8.8 ml/kg/min, respectively. In their sample, children with JIA had a VO_2 peak of 32.24 ml/kg/min, indicating that our sample was quite fit (Takken et al., 2002). When VO_2 was expressed per kg of fat free mass, an increasingly common practice for children, we found no significant differences between each of the groups.

Max power output was also significantly different between the groups. As there was a large variability in terms of participant size and age, it was inevitable that maximal power output was significantly different between each group. Power output for participants was predetermined to be around 3 W/kg body mass. This was adjusted for children that were less fit and could not pedal for the prescribed 8-12 minutes with that load. Overall, children with JIA had an average power output of 2.9±0.7 watts, and 2.9±0.7 watts for children with IBD, compared to 3.3±0.7 watts for healthy controls.

Muscle data for the groups were also in line with those found in the current literature. Grip strength was found to be higher in healthy children, but this was not statistically significant until expressed relative to body mass. In a study by Rashed et al., 2018, handgrip strength as measured with a dynamometer was 13.7±6.6 kg for children with JIA, and 20.5±5.7 kg for healthy controls. Again, our sample appeared to be significantly stronger with children with JIA at 21.1±6.3 kg and 29.4±11.5 for healthy controls. Grip strength expressed relative to body mass was significantly higher in healthy controls at 0.5±0.1 kg per kg body mass compared to children with JIA, 0.4±0.1. These values were found to be significantly lower than values found in healthy Canadian children ages 6-19 years with an average grip strength of 0.9±0.1 kg/kg body mass (Colley et al., 2019). Isometric flexion and extension were approaching significance with higher force produced by healthy controls compared to children with JIA or IBD. Isokinetic strength at all speeds including 60 deg/s and 180 deg/s, were significantly higher in healthy controls. Normative values for isokinetic knee flexion and extension, for children aged 10-19 at 60 deg/sec, show knee flexors exert a force of 89.8±34.6 N*m, and knee extensors exert a force of 152.8±71.1 N*m, on average

(McKay et al. 2017). This is in line with our sample where for peak torque flexion, healthy controls reached 184.0±76.5, and 83.2±41.8 N*m for peak torque extension at 60 deg/sec. However, due to different equipment and methodology used for measuring muscle strength, it is difficult to directly compare our findings to previous findings.

Rate of fatigue was calculated for flexion and extension for each group. Interestingly, the control group had the highest rate of fatigue for both extension and flexion. This could be explained by the fact that healthy controls started with a higher maximal force output and therefore had a higher decrease in strength over time relative to baseline strength. This also provides some insight into the fact that children with JIA or IBD may be experiencing feelings of fatigue, however physiologically, their muscles not experiencing fatigue faster than healthy children. Indeed, their rate of muscle fatigue as objectively measured over a series of 50 consecutive kicks is lower compared to healthy controls. A possible explanation for this is that as children with a chronic condition are exercising and moving at lower intensities, this is training their muscle endurance. This consideration of objectively measured fatigue is quite novel in children with JIA or IBD. In adults with Crohn's disease, it has been shown that they fatigue much sooner than healthy controls. Further investigations into this topic is required to confirm or refute this finding.

4.5 Inflammatory Blood Marker Activity in Children with JIA or IBD

Pro-inflammatory markers such as CRP, TNF-a, and IL-6 are implicated in many aspects of disease including impaired metabolic flexibility, leading to more prompt feelings of fatigue (Bourdier et al., 2019). Inflammatory markers are also implicated in

muscle wasting which may require children to put in extra work for the same amount of effort. Inflammatory markers were not significantly different between controls and children with JIA or IBD, apart from TNF-a. TNF-a was significantly elevated in children with IBD however, still remain in the bounds of normal. This indicates that our cohort has managed their disease activity relatively well and are not in a severe stage in their condition. Furthermore, a composite score of different inflammatory markers was created and it was found that IL-6 was significantly different compared to healthy controls. This is different from what was shown when the individual markers were analyzed with JIA and IBD separately. An explanation for this is that when the markers are expressed as a composite score, it is expressed relative to the mean of the sample. This indicates that the average IL-6 concentration was significantly different between the groups.

The markers chosen are acute phase reactants which are inflammatory markers that increase or decrease during times of acute injury or inflammation. This also shows that there were no significant signs of inflammation at the time of assessment.

4.6 Physical Activity and Fitness in Children with a Chronic Condition and Healthy Controls

When the samples for children with JIA and IBD are pooled, a similar picture appears. With respects to PA, a significant difference remains in the time spent in MVPA for these children with a chronic condition, compared to healthy controls. This supports findings from a recently published meta-analysis by Bourdier et al. Regardless

of methodology, both subjective (diaries and questionnaires) and objective (accelerometers) show children with JIA and IBD engage in less MVPA.

Aerobic fitness is significantly decreased in children with a condition when expressed relative to body weight. While the patterns appear consistent, our sample appear to be more fit compared to a previous study done by Ploeger et al. in children with IBD where their mean VO_2 peak value was 36.0±7.0 ml/kg/min. Mean peak power output in terms of wattage were also comparable at 3.0±0.7 and 2.9±0.8 for our sample.

A composite measure of strength showed that healthy controls had significantly higher isometric, isokinetic, and total composite strength compared to children with IBD or JIA. These differences were more pronounced when expressed relative to body mass. This is in line with the individual results found in the current literature.

4.7 Relationship between Self-Perceived Health and Well-being and PA in Children with JIA or IBD

A linear regression established that average MVPA per day could statistically significantly predict self-perceived health, $F(1,50) = 6.516$, $p = 0.014$ and MVPA accounted for 11.5% of the explained variability in self-perceived health. The regression equation was as follows: self-perceived health = 3.10 + 0.012*(average MVPA/day). This study is the first of its kind examining these relationships in children with JIA or IBD. In a recent study in healthy European children PA was found to be positively associated with self-reported health status (Granger et al., 2017). This was further expanded on in another study with children aged 7-14 years. Participants were asked to rate their health and had their PA measured using accelerometry. Here, they found that

general activity or sedentary behaviour was more predictive of health rather than any particular intensity of PA (Husu et al., 2016). This is contrary to our results as we found that average time spent in MVPA was significantly related to perceived health and well-being, rather than TPA. This might indicate that for children with a chronic condition, whether or not they engage in higher intensities of physical activity is more indicative of their self-perception of health. Additionally, children with a chronic condition may shy away from intense physical activities for fear of pain exacerbation. However, if they are able to get over this fear and participate in activities that are more intense in nature, they would consider themselves to be doing better in health. This idea was supported by recent research done in adults. Von Rosen and Hägstromer used a composition data analysis approach on accelerometer data to find that participants with poor, compared to excellent health, spend about a third of the time in MVPA (17 vs. 50 min/day). Furthermore, the data in the current study was not stratified by age or sex as no significant interactions were found in relation to self-perceived health and well-being, with p values ranging from 0.92 to 0.130 for different models. This finding supports work in self-perceived health by Waller et al., in which no significant interactions were found with age and sex.

In terms of perceived well-being, MVPA as a percentage of wear time could statistically significantly predicted 10.7% of the explained variability in self-perceived well-being. This was in line with results on PA and well-being in school age children in Ireland. Children who were getting the recommended levels of MVPA (at least 60 min/day) scored significantly higher on measures of well-being than less active children (Breslin et a., 2017). Contrary to our findings, Edmunds et al. investigated this

relationship in 36 children with type 1 diabetes and found no significant associations between self-perceived well-being and physical activity. However, in that study, physical activity was monitored using a heart rate monitor. Heart rate as an objective measure of PA, has been found to have a strong linear relationship with energy expenditure across moderate and vigorous intensities, however, this relationship is not as strong in the light intensity range (Ainsworth et al., 2015). For this reason, the researchers may not have captured an accurate picture of the participant's PA.

4.8 Relationship between Self-Perceived Health and Well-being and Fitness in Children with JIA or IBD

Linear regression models found some fitness variables were able to statistically significantly predict self-perception measures. However, only power output relative to body mass was able to predict of self-perceived health, $F(1,53) = 5.148$, $p= 0.027$, where relative maximal power output accounted for 8.9% of the variability seen in self-perceived health. Currently this is one of the first studies to look at this relationship in children with JIA or IBD. In other studies, where this has been explored in healthy children, there is a consensus that children who have higher cardiorespiratory fitness, perceive themselves to be healthier. In one study, in a sample of 7402 children ages 9-17, they found self-perceived health was associated with cardiorespiratory fitness as measured by the FITNESSGRAM in both genders. The FITNESSGRAM is a battery of fitness assessments that include aerobic and muscular fitness. For aerobic fitness, a VO_2 peak is estimated from PACER (Progressive Aerobic Cardiovascular Endurance Run), essentially the "beep test", a one-mile run, and a walk test (Velez et al., 2017).

This relationship was also measured in 533 adolescent girls with obesity. Girls who were classified as unfit as determined based on the FITNESSGRAM were more likely to report negative self-rated health in univariate analyses and multivariate analyses. Obese girls were more likely to report negative self-rated health compared to their normal-weight peers; however, these associations were lost in multivariate analyses, suggesting an effect of fitness (Mota et al., 2012). These relationships were supported in numerous studies looking at fitness and self-rated health in healthy school age children (Eriksen et al., 2013; Gualteros et al., 2015). In line with our sample, a study by Malleson et al., in 1996 on 31 children aged 8-17 found no relationship between peak VO_2 uptake, and self-rated health perceptions, only relative power output. A possible explanation for this is that PA is a behaviour, something to participate in and therefore easily influenced by how one is feeling on a particular day. While maximal power output is a measure of fitness, motivation to continue pedaling is variable depending on the day, and therefore more likely to be affected by self-perceived health. On the other hand, VO_2 peak is more of a biological measure, accurately measuring an adaptive state and therefore less malleable to day-to-day changes. Therefore, changes in self-perceptions of health are unlikely to affect VO_2 peak in this population.

On the other hand, fitness was a stronger predictor of self-perceived well-being, particularly relative VO_2 peak, $F(1,38) = 6.683$, $p = 0.014$, where relative VO_2 peak accounted for 15% of the variability with self-perceived well-being. As the idea of self-rated health is quite novel in children with a chronic condition, there is no literature on this topic. Interestingly, these results are in line with the current literature in self-perceived health in healthy children as seen above. A possible explanation for this

result is due to the fact that perceived well-being is more of a global assessment that asks children to indicate how well they are doing with respect to disease and all the ways that their disease may affect them as compared to self-rated health, which simply asks the children to simply rate their health in general, which is more prone to recency effects. Based on these results, in relationship to their condition, if children consider themselves to be doing well, they are therefore more likely in engage in activities that are more vigorous in nature, thus improving fitness.

In terms of muscle strength, composite scores for strength were not found to be predictive of any measures of self-perceived health or well-being. As this is a novel idea, there is some preliminary research done on this topic in adults. Isometric muscle strength as assessed by maximal handgrip strength and repeated chair stand test was calculated for regression odds ratio along with self-rated health. Again, greater muscle strength was positively associated to better self-rated health. However, in this population they also found the same association to higher levels of MVPA (Hansen et al., 2013). This may be explained by that fact that children with a chronic condition are less likely to engage in intensities of MPA or VPA and are therefore less likely to work at the intensity required to build muscle strength.

4.9 Relationship between Inflammatory Markers, PA and Fitness in Children with JIA or IBD

Studies that assessed levels of PA relative to disease activity found that children with active disease had a lower PA level than children in remission, suggesting that the activity of the disease was the main deterrent to PA for children with JIA or IBD (Cavallo

et al., 2015). In the current study, with regards to clinical inflammatory markers as a measure of disease activity, only relative composite isometric strength was found to significantly statistically predict an inflammatory blood marker composite score. Lee et al., 2018 examined 138 children aged 14.2 ± 2.8 with IBD for muscle strength and various markers of disease activity. In their sample, TNF-a was independently associated with an isometric muscle torque z-score. In our sample, even with active disease, most of the children that agreed to participate in the study managed their disease very well. Therefore, the inflammatory markers were not significantly elevated, and were comparable to healthy controls. As such, our findings could not provide a clear picture on how PA and fitness are truly affected by inflammatory blood markers and more research in this area is required to delineate the specific effects of inflammatory markers on muscle strength.

4.10 Exploratory Analyses

The exploratory portion of this thesis examined whether there was a relationship between objectively measured muscle rate of fatigue in comparison to self-received ratings of health and well-being, as well as inflammatory blood markers. The pervasive nature of sickness symptoms even into remission prompted this investigation (Ringold, Ward, & Wallce, 2013; Ambrust et al., 2016). Whether or not there was a physiological explanation for the feelings of fatigue and pain is an important aspect to investigate. The idea of objectively measured muscular fatigue in patients with IBD was put forth by van Langenberg et al. in 2014. They found that subjective measures of physical fatigue were correlated ($r = -0.52$, $p < 0.05$) to objectively measured muscular fatigue. While self-

perceived fatigue was not explicitly measured in our study, it is thought that the self-perceived health and well-being measures would be a good proxy measure. The inflammatory marker TNF-a was able to statistically significantly predict the rate of fatigue for flexion. TNF-a accounted for 18.4% of the variability with rate of fatigue for flexion. TNF-a approached significance when predicting rate of fatigue for extension, explaining 8% of the variability. This is in line with the current literature as higher plasma levels of inflammatory markers is known to result in a greater severity of muscle fatigue (van Langenberg et al., 2014). No significant relationship was found with the self-perceived health or well-being measures based on linear regression models. In the future, specific questionnaires targeting fatigue should be used with regards to investigation of the relationship between these variables. Understanding whether there is a significant relationship could allow us to understand whether sickness behaviours are due to psychosocial or physiological factors.

4.11 Novelty of Findings

The goal of this thesis was to investigate the relationship between self-perceived health and well-being, and physical activity and fitness. An additional goal was to determine if inflammatory blood markers (as a proxy for disease activity) could be predicted by physical activity and fitness. These analyses involved first understanding whether there was a significant difference in our sample with regards to self-perceived health and well-being, physical activity and fitness, and inflammatory markers between children with JIA or IBD, and healthy controls. Then, whether or not these variables were predictive of self-perceived health and well-being, and inflammatory blood markers

amongst children with a chronic condition. This thesis established several novel findings:

1. The relationship between physical activity and fitness was investigated with respect to self-perceived health and well-being in children with JIA or IBD. We observed that there were significant relationships between self-perceived health and well-being with MVPA. Furthermore, significant relationships were found between these measures and aerobic fitness.
2. Physical activity levels were quantified objectively using an accelerometer and showed that children with a stable condition may not necessarily be less active than their healthy peers. However, our sample did engage in lower amounts of moderate to vigorous intensity physical activity. This is an important update to the current field of literature as the focus needs to shift to go a step beyond PA in general, and to help children with JIA or IBD be engaged in more moderate to vigorous physical activity.
3. In children with a chronic condition such as JIA or IBD, the relationships between self-rated health and muscle strength/musculoskeletal fitness were investigated. Muscle strength is a crucial component of fitness that often takes a backseat to aerobic fitness. While no significant relationships were found in relation to self-perceived health and well-being and muscular strength, these findings still expand on current knowledge on the topic. Significant relationships between these variables may not have been seen due to the fact that children with JIA or IBD engage in less moderate to vigorous PA which may not be enough to elicit changes in fitness.

Furthermore, it expands the literature in relation to isometric and isokinetic muscle strength in children with JIA or IBD. It was found that children with JIA or IBD are indeed weaker in their dominant leg compared to healthy controls for all measures of isometric and isokinetic flexion and extension. This area of research is quite scant with respect to this topic.

4. Previous studies that have assessed levels of PA relative to disease activity suggest that disease activity is the main deterrent to PA for children with JIA or IBD. This thesis shows that even without any signs of clinical inflammatory blood markers, children with JIA or IBD engage in significantly less levels of MVPA and have lower aerobic and musculoskeletal fitness compared to healthy controls.

4.12 Limitations

This thesis investigated novel relationships between self-perceived health and well-being with health outcomes such as PA and fitness. While the health outcomes were measured using objective methodology (for physical activity, aerobic fitness, and muscle strength), the accuracy of the results is influenced by the cooperation of the participants. This is often the first time the participants are made to undergo intense maximal testing which can be daunting leading to failure at submaximal intensities. Particularly in this population, it may be pain that the participants may not be used to and therefore interpret it as a sickness symptom. The downside of this was missing or invalid data due to an incomplete maximal test. The assessors worked hard to encourage the children throughout the session.

The relationships from this thesis were made from cross-sectional data collected at one time point. Therefore, only correlational relationships can be drawn, and we are unable to infer causality. A larger scale study that took into account various confounding factors that affect self-perceived health and well-being, over time may be able to form stronger conclusions. A longitudinal study would be able to provide various time and data points to be able to accurately examine the relationships more holistically.

Accelerometers are a widely used instrument in the assessment of PA in children. PA assessments were only completed at one time point so results may have been related to the season their study visit was in. Furthermore, the devices are not waterproof and therefore cannot be worn in the pool. Therefore, any activity that may have accumulated there would have been missed. This is particularly regretful for children with JIA, where aquatic activities are encouraged as it has less strain on the joints (Houghton, 2012).

Another limitation is with regards to sample size for the study. The complete patient population for JIA or IBD at our children's hospital was not tested. Therefore, our results may not be applicable to the general JIA or IBD population, particularly those with active disease. Based upon our samples in comparison to values that are currently in the literature, it appears that our sample is more fit and active than the average child with JIA or IBD.

With regards to assessment of clinical disease activity, inflammatory blood markers were used as a proxy, rather than compiling a score such as is the practice with the JADAS, and PUCDAI and PCDAI. This was due to the fact that there was an incomplete data set for this variable. However, clinical disease activity measures such

as disease duration (in years) and medication usage were obtained through a medical questionnaire.

4.13 Future Directions

This study provides a novel examination of self-perceived health and well-being data and contributes to understanding these variables in relationship to various PA and fitness outcomes. This area of research is still in its infancy with regards to the children with JIA or IBD and requires further contributions. Future studies would benefit from recruiting children with both low and high levels of disease activity to provide a more comprehensive idea of the relationships. Children living with a chronic condition are a vulnerable population that requires further research into ways to better manage sickness symptoms that persist even into remission. The exploratory analyses of this thesis looked at the measurement of fatigue, specifically. More specific questionnaires or even methods that can measure specific subcategories of health and well-being (ex. pain, fatigue, mood, quality of life, etc.) particularly those based around sickness symptoms may be able to yield more data as to which aspects are preventing children from being physically active and fit. Only then, can we get an idea of the direction to develop targeted therapeutic approaches to improve PA and fitness in this population to decrease the risk for the development of secondary conditions.

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Appendix A: Parent/Guardian Consent Form

McMaster University Health Sciences

Hamilton Health Sciences
EXEMPLARY CARE • ACADEMIC EXCELLENCE

PARENT CONSENT FORM

Title of Study: Cardiovascular Health in children with a chronic inflAMmatory condition: role of Physical activity, fItness, and inflammatiON

Local Principal Investigator: *Dr. Brian W. Timmons (PhD), Pediatrics*

Principal Investigator: *Dr. Joyce Obeid (PhD), Pediatrics*

Co-Investigators: *Dr. Maureen MacDonald (PhD), Kinesiology*
Dr. Tania Cellucci (MD), Pediatrics
Dr. Lehana Thabane (PhD), Clinical Epidemiology & Biostatistics

Funding Source: **Heart & Stroke Foundation**

INTRODUCTION

Your child is being invited to participate in a research study conducted by Dr. Brian Timmons and colleagues because they have been diagnosed with one of the following conditions: cystic fibrosis, juvenile idiopathic arthritis, chronic kidney disease, inflammatory bowel disease, or type 1 diabetes. In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form gives detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate. Your child will be asked to sign another form to confirm that they agree to participate. Take your time to make your decision.

WHY IS THIS RESEARCH BEING DONE?

We know that heart disease can start in childhood. But because children hardly ever get heart attacks, so-called risk factors can be measured to guess which children might eventually develop heart disease. We are also learning that children growing up with a medical condition may be at even greater risk for heart disease, although we have a lot more to learn. This is a problem that we will begin to examine in this project. We don't know if the problem is because of their medical condition or because of lifestyle factors, such as not getting enough exercise, or a combination of both. In this project, we will study some of the most common diseases that children get: cystic fibrosis, juvenile arthritis, kidney disease, inflammatory bowel disease, and type 1 diabetes. Doctors need to know if their patients are at risk for getting heart disease. This could stop heart disease or at least reduce its impact because we may be able to intervene with the right therapy at the right time. By studying these patients together, we will quickly learn a lot about heart health for these children who are now living longer than ever before.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to compare heart health in children diagnosed with a medical condition and healthy children. We also want to see if heart health in our patients is related to physical activity, fitness, and inflammation. Inflammation is when the body's immune system

doesn't work properly and this is probably not good for heart health. If we find that any of these factors are related to heart health, then we can design studies to test whether changing them will be good for health in our patients.

WHAT WILL MY CHILD'S RESPONSIBILITIES BE IF THEY TAKE PART IN THE STUDY?

If you volunteer to participate in this study, we will ask your child to visit the Child Health & Exercise Medicine Program laboratory at the McMaster Children's Hospital on two occasions, separated by 1 or 2 weeks, to perform the following things:

- **Visit #1:** This visit will take a total of 3 hours and can be scheduled at your convenience, in either the evening, after school, or on weekends. During this visit, we will measure the following things:
    1) **Body composition assessment**: To determine how much muscle and fat is in your child's body, we will have them stand on a special machine. There is a small electric current that is passed through their body but they will not feel it because it is so small.
    2) **Aerobic fitness test**: This test requires your child to ride on our stationary bicycle for about 12 minutes – during the test it will feel like they are riding up a hill and the hill is gradually getting steeper and steeper. During the whole test, they will breathe through a mouthpiece connected to a machine that tells us how much oxygen the body is consuming. This mouthpiece feels like a mouth guard they might wear during sports or a snorkel. We use this information to determine aerobic fitness, because more fit children can use more oxygen during this test.
    3) **Muscle strength test**: During this test your child will be asked to do a series of kicking exercises and we will measure their muscle power during the exercise.
    4) **Questionnaires**: Between fitness tests when your child is resting, we will have them and you fill out some questionnaires that tell us about their physical activity and the issues they see as important for getting or not getting enough exercise. We will also ask you to complete a few questionnaires to better understand your background and your child's disease history. Some of these questionnaires will ask about how your child feels, and may seem personal. We ask that you complete these to the best of your knowledge. All of your answers will be kept strictly confidential. You should also know that you can choose not to answer any questions that make you feel uncomfortable, this will not affect your child's participation in the study.
    5) **Physical activity assessment**: Before leaving the laboratory, we will give your child a small pager-like device to wear for the next 7 days in a row – this device monitors physical activity. They can take it off only if they are going to get wet (like in the bathtub or swimming) and at bedtime. We request that you write down in a diary, that we will provide, the times that it is taken off and put back on. We will ask you to return the monitor at your second visit. At that time, we will have a few questions to ask you and your child about any issues that might have arisen while wearing the device for the 7 days.

- **Visit #2:** This visit will also take about 3 hours to complete. We will ask that your child come in to the lab in a fasted state for this visit (no food or drink for 10 hours), so we will schedule this visit in the morning either before school or on the weekend. During this visit we will measure the following things:
    1) **Cardiovascular health:** We will measure the health of the main blood vessel in your child's neck. This test requires your child to lie on a bed for about 15 min for the measurements to be taken. This will be followed by an assessment of how well your child's blood vessels work. To do this, we will ask them to lie on a bed and we will place a blood pressure cuff on their arm, this will be inflated for 5 minutes and then deflated, and we will take images of how the blood vessel in their arm reacts to the blood pressure cuff.
    2) **Blood sample:** A small, 40 mL (about 2.5 tablespoons) blood sample will be taken to allow us to measure some cells in the blood that have been linked with cardiovascular health. Your doctor also measures most of these cells when your child has their regular blood work done. If your child is having regular bloodwork done for their clinic visit, please notify the research coordinator and we will try to schedule the study bloodwork to happen with their clinic visit.
    3) **Motor skills test**: This test will take about 15 minutes and will help us assess your child's motor skills by asking them to drawing, balancing, running, and ball-throwing tasks.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

There are no risks or discomforts to measuring body composition. The tests of fitness and muscle power require an all-out effort so people generally feel tired after this test. The test of aerobic fitness also requires your child to keep pedaling until they can no longer keep going. This test measures fitness by seeing how hard the heart, lungs, and muscles can work together. There is a small chance (about 3 in 10,000) that your child may faint after the test of aerobic fitness. However, young people tend to recover very quickly. We will give your child lots of rest before the next test. Wearing the physical activity monitors should not pose any risks or discomforts for your child, nor should completing the questionnaires. The assessment of cardiovascular health is done with the same ultrasound machine that doctors use to take a picture of a baby during a pregnancy. Your child may experience some discomfort when the blood pressure cuff is inflated, but this will be very minor and temporary (until the blood pressure cuff is deflated). An experienced investigator will collect a blood sample during your child's second visit that will be similar to the samples your child routinely gets for clinic. A small bruise may appear where the needle goes through the skin. While it is very rare, there is also a chance that your child may feel light-headed after the blood sample. We will have snacks and water on hand to minimize the risk of this happening, but taking this amount of blood will have no major negative effects.

HOW MANY PEOPLE WILL BE IN THIS STUDY?

We are asking a total of 180 children and adolescents to participate in this study. Your participation is voluntary.

WHAT ARE THE POSSIBLE BENEFITS FOR MY CHILD AND/OR FOR SOCIETY?

We cannot promise any personal benefits to you or your child from their participation in this study. We will make each visit fun and enjoyable for your child. You will learn about your child's physical activity and fitness. This information could provide us with information on areas that your child can work on improving. Your participation will be very important for us to learn how best to address physical activity, fitness, and heart health in other young children with chronic disease and to design programs that can help in these areas of health

WHAT INFORMATION WILL BE KEPT PRIVATE?

All of your child's information will be stored in locked filing cabinets under the supervision of Dr. Brian Timmons for 10 years. **To be able to understand the results of this study, we will need to obtain some of your child's medical information. For example, types of medication they are taking, how long they have had their disease, etc. We can obtain this information from your child's medical chart from the doctor who is responsible for the care of your child's disease. We will not record your child's health card number or any other information that could identify your child.** We will supervise access to your child's information by other people in our group, only if necessary. Your child will be assigned a subject number used to identify them. Records identifying your child will be kept confidential. If the results of the study are used in a presentation, your child's identity will remain confidential.

CAN PARTICIPATION IN THE STUDY END EARLY?

If you and your child volunteer to be in this study, you or your child may withdraw at any time with no prejudice. The investigator may withdraw you from this research if circumstances arise which warrant doing so. In no way will withdrawing from this study affect the care you receive from your specialist.

WILL MY CHILD BE PAID TO PARTICIPATE IN THIS STUDY?

We will provide your child $50 as reimbursement for their participation in this study. If you quit the study for personal reasons, we will change the amount for the time completed. If you choose to quit because of a complication from the study, we will give you the full amount. We will pay for your parking expenses at the McMaster Children's Hospital. We will also provide you with a 1-page report of the findings and what they mean.

IF I HAVE ANY QUESTIONS OR PROBLEMS, WHOM CAN I CALL?

If you have any questions about the research now or later, or if you think you have a research-related injury, you can contact Joyce Obeid at our research office at 905-521-2100 extension 73517 (Daytime) or at 905-928-5538 in the evenings, you can also contact Dr. Brian Timmons directly at 905-521-2100 extension 77218 or 77615.

If you have any questions regarding your rights as a research participant, you may contact Deborah Mazzetti (Manager) at the Hamilton Integrated Research Ethics Board at 905-521-2100 extension 42013.

CONSENT STATEMENT

I have read the preceding information thoroughly. I have had the opportunity to ask questions, and all of my questions have been answered to my satisfaction and to the satisfaction of my son and/or daughter. I agree to allow my child to participate in this study entitled: *"Cardiovascular Health in children with a chronic inflAMmatory condition: role of Physical activity, fItness, and inflammatiON: The CHAMPION Study"*. I understand that I will receive a signed copy of this form.

Would you like to be contacted by Dr. Timmons or a member of the Child Health & Exercise Medicine Program research team with information about future studies other than the one described in this consent form? Any future studies would be approved by the Research Ethics Board, and would require you to sign a new consent form. **Please note we will only contact you if your child is eligible for a maximum of 2 times per year.

☐ Yes, please contact me. ☐ No, please do not contact me.

_____
Name of Participant (child's name)

_____
Name of Legally Authorized Representative

_____ _____
Signature of Legally Authorized Representative Date

Consent form administered and explained in person by:

_____
Name and title

_____ _____
Signature Date

SIGNATURE OF INVESTIGATOR:

In my judgement, the participant is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent for their son and/or daughter to participate in this research study.

_____
Name and title

_____ _____
Signature of Investigator Date

FUTURE RESEARCH

At the end of the study, we may wish to store leftover sample for use in a future study. We will not store your child's sample longer than 10 years. All records identifying your child will remain confidential. Information about your child will not be released. If the results of the study are published, your child's identity will remain confidential.

CONSENT STATEMENT FOR STORAGE OF SAMPLES (BLOOD)

I have read the preceding information thoroughly. I have had the opportunity to ask questions, and all of my questions have been answered to my satisfaction and to the satisfaction of my son and/or daughter. I agree to have my child's blood stored so it can be used for future research studies approved by the Research Ethics Board other than the one described in this information form.

_____
Name of Participant (child's name)

_____
Name of Legally Authorized Representative

_____ _____
Signature of Legally Authorized Representative Date

Consent form administered and explained in person by:

_____
Name and title

_____ _____
Signature Date

SIGNATURE OF INVESTIGATOR:

In my judgement, the participant is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent for their son and/or daughter to store blood.

_____
Name and title

_____ _____
Signature of Investigator Date

McMaster University Health Sciences

Hamilton Health Sciences
EXEMPLARY CARE • ACADEMIC EXCELLENCE

PHOTO, AUDIO AND VIDEO RELEASE FORM

I, _____, hereby give McMaster University's Faculty of Health Sciences my permission to take and use any photographs, movie films, audio or video tapes made of my child, (name) _____, taken on (date) _____, and I consent to the reproduction of same in any proper manner whatsoever for possible publication and I hereby waive any rights that I may have in such photographs, movie films and audio or video tapes or reproductions of same.

I hereby release McMaster University's Faculty of Health Sciences, its employees, agents, servants and attending physicians from all actions, causes of actions, claims and demands arising out of such consent.

Notice of collection of personal information

By taking my photograph, whether by still photograph, film or video and/or taping my voice, I acknowledge that McMaster University is collecting my personal information as defined by the Freedom of Information and Protection of Privacy Act of Ontario (RSO 1990).

The personal information is collected under the authority of The McMaster University Act, (1976). The information is used for public relations purposes of the Faculty of Health Sciences including, but not limited to, publications, websites and materials promoting McMaster University. Personal information will not be used for any unrelated purpose without prior consent. This information is protected and is being collected pursuant to section 39(2) and section 42 of the Freedom of Information and Protection of Privacy Act of Ontario (RSO 1990). Questions regarding the collection or use of this personal information should be directed to the Manager, Public Relations, Faculty of Health Sciences.

I, _____, represent that I am the parent or guardian of the minor named above and that I have the legal authority to execute the foregoing consent and release, and hereby approve the foregoing, and waive any rights in the premises.

Name of Participant	Signature of Participant	Date
Name of Parent/Guardian	Signature of Parent/Guardian	Date
Name of Witness	Signature of Witness	Date

Appendix B: Medical Questionnaire

MEDICAL QUESTIONNAIRE

Study ID: _____

Date of Birth: _____

1. Does your child have any of the following conditions (circle each of the appropriate):
   a) Heart disease
   b) High blood pressure
   c) Loss of consciousness
   d) Asthma
   e) Intestinal disease
   f) Surgery or fractures
   g) Allergies
   h) Diabetes Type 1 or 2
   i) Epilepsy
   j) Arthritis
   k) Cystic fibrosis
   l) Inflammatory bowel disease
   m) Chronic kidney disease
   n) Developmental condition (ADHD, Autism, etc.)
   o) Other: _____
   i) None

2. If your child is diagnosed with any medical condition, do you recall their date of diagnosis?

3. Present health:
   a) Good
   b) Complaints: _____

4. When thinking of prior exercise involvement, has your child experienced (circle the appropriate):
   a) An inability to keep up with other children
   b) Chest pain
   c) Fainting
   d) Dizziness
   e) Irregular heart beat
   f) Wheezing
   g) Other: _____
   h) None of the above

5. Has your physician ever suggested that your child restrict their levels of physical activity?
   ☐ Yes
   ☐ No

6. Do you know of any medical reason that would prevent your child from participating in physical activity?
   ☐ Yes. Please specify: _____
   ☐ No

MEDICAL QUESTIONNAIRE

Study ID: _____

7. Is your child currently taking any medications (please include any puffers, enzymes, vitamins, natural supplements, and oral contraceptives)? If yes, how frequently?

Medication	Frequency

☐ My child is not currently taking any medications

8. Has your child taken any other medications or had any medication changes in the past month? If yes, how frequently?

Medication	Frequency

☐ My child has not taken any medications in the past month

Appendix C: Physical Activity Log

Child Health & Exercise Medicine Program

ACCELEROMETER DIARY:

In addition to wearing the accelerometer for one week, we ask that you keep this log to monitor the times the accelerometer was put on or taken off, and the activities that you participated in when wearing the accelerometer. This will help us to understand your regular physical activity. Please bring this form along with your accelerometer to your next study visit.

Event	Example	DAY 1 Day: _____ Date: _____	DAY 2 Day: _____ Date: _____	DAY 3 Day: _____ Date: _____	DAY 4 Day: _____ Date: _____	DAY 5 Day: _____ Date: _____	DAY 6 Day: _____ Date: _____	DAY 7 Day: _____ Date: _____
Time the device was put on	8:02 AM							
Times the device may have been taken off and put back on and reason(s) (e.g. nap, swimming, shower, etc)	4:45 pm – 5:27 pm (Nap)							
	7:10 pm – 7:37 pm (Shower)							
	-							
	-							
Time the device was taken off before bed	10:19 pm							
Activities (e.g. soccer, camp, game)	- Walked to school - Played outside - Soccer practice - Bike ride							

ID: _____

ACCELEROMETER #: _____

PLEASE SEE THE NEXT PAGE FOR DETAILED INSTRUCTIONS

Appendix D: Patient's Global Assessment

CHAMPION Study
CHAQ, Y7-17

Study ID: CHAMP - _ _ - _ _
Date: _ _ - _ _ _ - _ _

Are you able to…	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do	Not applicable
30. Ride a bike?	☐	☐	☐	☐	☐
31. Do household chores (e.g., wash dishes, take out trash, vacuum, yardwork, make bed, clean room)?	☐	☐	☐	☐	☐
32. Run and play?	☐	☐	☐	☐	☐

33. Please check any **aids or devices** that you usually uses for any of the activities mentioned above:

☐ Raised toilet seat
☐ Bathtub seat
☐ Jar opener (for jars previously opened)
☐ Bathtub bar
☐ Long-handled appliances for reach
☐ Long-handled appliances in bathroom (such as a brush for washing)
☐ Other, please specify: _____
☐ None

34. Please check any categories for which you usually need **help from another person because of illness**:

☐ Hygiene ☐ Gripping and opening things ☐ Reach ☐ Errands and chores
☐ None

35. We are interested in learning whether or not you have been affected by pain because of your illness. How much pain have you had **because of your illness in the past week**? Place a mark on the line below to indicate how severe your pain is:

No Pain ——————————— Pain as bad as it could be

36. **Overall well-being:** Considering all the ways your disease affects you. Please rate how you are doing by placing a mark on the line below:

Doing very well ——————————— Doing very poorly

Appendix E: Self-Perceived Health Scale

CHAMPION Study
KIDSCREEN-27, Y7-17

Study ID: CHAMP - _ _ - _ _
Date: _ _ - _ _ _ - _ _

This questionnaire asks about you, how you feel, and what you like to do. This is not a test, and there are no right or wrong answers. Some questions may seem personal and some are about things not everybody does. Take your time and please be sure to answer each question based on what you really think. Your answers will be kept private (will not be shared with your parents or doctors without your permission). You can choose whether or not to answer certain questions. You can also choose whether or not to fill out this questionnaire. If you have any questions, you can ask us at any time.

A. Physical Activity and Health

1. In general, how would you say your health is?
   - ☐ Excellent
   - ☐ Very good
   - ☐ Good
   - ☐ Fair
   - ☐ Poor

Thinking about the last week:	**Not at all**	**Slightly**	**Moderately**	**Very**	**Extremely**
2. Have you felt fit and well?	☐	☐	☐	☐	☐
3. Have you been physically active?	☐	☐	☐	☐	☐
4. Have you been able to run well?	☐	☐	☐	☐	☐

Thinking about the last week:	**Never**	**Seldom**	**Quite often**	**Very often**	**Always**
5. Have you felt full of energy?	☐	☐	☐	☐	☐

B. General Mood and Feelings about Yourself

Thinking about the last week:	**Not at all**	**Slightly**	**Moderately**	**Very**	**Extremely**
6. Has your life been enjoyable?	☐	☐	☐	☐	☐