INVESTIGATING TRADITIONAL AND EMERGING CARDIOVASCULAR DISEASE RISK FACTORS IN PEDIATRIC POPULATIONS WITH CHRONIC INFLAMMATORY DISEASE

INVESTIGATING TRADITIONAL AND EMERGING CARDIOVASCULAR DISEASE RISK FACTORS IN PEDIATRIC POPULATIONS WITH CHRONIC INFLAMMATORY DISEASE

By

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TITLE: Investigating novel and emerging cardiovascular risk indicators in pediatric populations
with chronic inflammatory disease

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ABSTRACT

For most children, occult vascular damage is minimal and has a slow rate of progression likely due to the existence of healthy lifestyles and the prevalence of preventative behaviours. However, there is evidence to suggest a marked increase in the prevalence of traditional and emerging cardiovascular risk factors in children with chronic inflammatory conditions due to the common aetiology pathways of inflammation and atherosclerosis. In the current cross-sectional study, a comprehensive vascular assessment was conducted on 21 children with various chronic inflammatory conditions including juvenile idiopathic arthritis (JIA), cystic fibrosis (CF), type I diabetes mellitus (T1DM) and inflammatory bowel disease (IBD) (CIC, 12.7 ± 2.3 years) compared to 9 healthy, age and sex-matched controls (CON, 13.1 ± 1.8 years). B-mode ultrasound images were used to assess carotid artery intima media thickness (cIMT) as well as local arterial stiffness through measurement of compliance and distensibility with the use of concurrent applanation tonometry. Whole-body arterial stiffness was measured by assessing pulse wave velocity (PWV) between the carotid and dorsalis pedis arteries. A brachial flow mediated dilation (FMD) test was implemented to assess endothelial function of the brachial artery. Twelve hour-fasted blood samples were collected and analyzed for blood lipids and an acute inflammatory marker, C-reactive protein (CRP). There were no group differences in cIMT ($p=0.18$), distensibility ($p=0.40$), compliance ($p=0.88$), whole body PWV ($p=0.74$) or LDL-cholesterol ($p=0.99$). The CIC group demonstrated significantly lower FMD when

compared to CON (p=0.01). There were no group differences in inflammatory levels, as indicated by concentration of CRP (p=0.63). Sub-analyses revealed similar cIMT, distensibility, compliance, PWV and LDL levels between children with JIA (n=11, 12.6 ± 2.9 years), CON (n=9, 13.1 ± 1.8 years) and the other inflammatory conditions (INFL, n=10, 12.4 ± 1.7 years). Both JIA and INFL reported lower FMD when compared to CON (p=0.04). INFL had lower BMI compared to JIA and CON (p=0.02). The primary findings from this study suggest that arterial structure is similar between children with a CIC and their healthy peers; however, arterial function, as indicated by FMD (%), was reduced in the CIC group. This finding is essential in that it helps to identify an area for targeted intervention and/or prevention of future CV events as endothelial dysfunction is known to be an early event in the pathophysiology of atherosclerosis

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LIST OF ALL ABBREVIATIONS AND SYMBOLS

BMI	Body mass index
CV	Cardiovascular
CVD	Cardiovascular disease
cIMT	Carotid artery intima-media thickness
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial blood pressure
PWV	Pulse wave velocity
FMD	Flow mediated dilation
SR	Shear rate
CRP	C-reactive protein
LDL	Low-density lipoproteins
HDL	High-density lipoproteins
VLDL	Very-low-density lipoproteins
TC	Total cholesterol
TG	Triglycerides
VCAM-1	Vascular adhesion molecule-1
NO	Nitric oxide
ET-1	Endothelin-1
PAD	Peripheral artery disease
JIA	Juvenile idiopathic arthritis
RA	Rheumatoid arthritis
sICAM-1	Soluble intercellular adhesion molecule-1
CF	Cystic fibrosis
IL-8	Interleukin-8
IL-6	Interleukin-6
T1DM	Type 1 diabetes mellitus

HbA1c	Plasma hemoglobin 1Ac
ADA	American Diabetes Association
ISPAD	International Society for Pediatric and Adolescent Diabetes
AI	Augmentation index
IBD	Inflammatory bowel disease
UC	Ulcerative colitis
CD	Crohn's disease
TNF-∝	Tumor necrosis factor alpha
PCDAI	Pediatric Crohn's Disease Activity Index
PUCA	Pediatric Ulcerative Colitis Activity Index
CIC	Chronic inflammatory condition
ELISA	Enzyme-linked immunosorbent assay
DICOM	Digital Images and Communications in Medicine
AMS	Artery Measurement System
ROI	Region of Interest
PPG	Photoplethysmograph
AUC	Area under the curve
INFL	Other inflammatory condition (CF, T1DM and IBD)
TTP	Time to peak
RH	Reactive hyperemia

CHAPTER 1 - LITERATURE REVIEW

1.1 Cardiovascular disease

Cardiovascular disease (CVD) consists of several types of diseases pertaining to the heart and blood vessels and is the leading cause of death worldwide (Alwan, 2010). In fact, heart disease and cerebrovascular disease are the leading two causes of death following cancer (Public Health Agency of Canada, 2010). Data from the 2014 Canadian Community Health Survey indicates that 6% of Canadians 20 years and older are living with a CVD, a proportion that has remained stable since 2007 (Public Health Agency of Canada, 2016).

1.2 Cardiovascular disease in early life

Pathological studies have revealed that the presence and quantity of atherosclerotic lesions in children and young adults have a strong correlation with traditional CVD risk factors such as low-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure and body mass index (BMI) (Kavey et al., 2003). Studies in both children and adolescents have revealed that progression of atherosclerosis is largely mediated by the prevalence of these identified, premortem risk factors (Tuzcu et al., 2001; McMahan et al., 2005). For most children, occult vascular damage is minimal and cardiovascular events are rare likely due to the existence of healthy lifestyles and prevalence of preventative

behaviors (Kavey et al., 2003).

1.3 Arterial anatomy

Arteries are muscular tubes consisting of three distinct layers which are known as the tunicas intima, media and adventitia. The inner most layer, the tunica intima, is composed most notably of the endothelium and is accompanied by a thin layer of connective tissue, the lamina propia, and a fenestrated layer of elastic fibres known as the internal elastic membrane responsible for anchoring itself to the tunica media (Vanputte et al., 2014). The endothelium is a single layer of cells that lines the lumen of the artery and is a key player in regulating arterial physiology. It is primarily reactive to blood flowing through the artery that will exert a translation force on the cells known as shear force (Davies, 2009). The tunica media is the middle layer of the artery wall and is primarily composed of concentrically-arranged smooth muscle cells and provides the artery with its structural integrity (Vanputte et al., 2014). When the ring of smooth muscle cells contract, the artery constricts to reduce the quantity of blood flowing through the artery, a phenomenon known as vasoconstriction. Opposite to this, when the smooth muscle is allowed to relax, the diameter of the artery is allowed to increase which in turn increases the quantity of blood flow, known as vasodilation. The tunica adventitia contains a higher proportion of collagen fibres and serves to anchor to the tissue surrounding the arteries (Vanputte et al., 2014).

1.4 Initiation and Progression of the Inflammatory Process in Atheroma

When the endothelium becomes damaged, entry of low-density lipoproteins (LDLs) are enabled which may burrow in the intimal layer of the artery wall where they will become oxidized (Hahn et al., 2007). Oxidized LDLs activate endothelial cells to up-regulate the expression selective adhesion molecules such as the vascular cell-adhesion molecule-1(VCAM-1) (Montecucco & Mach, 2009). Adhesion molecules are responsible for binding various circulating blood leukocytes, namely monocytes and T-lymphocytes (Argyropoulou et al., 2003). Once bound to the endothelium, a group of chemoattractant cytokines will recruit the leukocytes into the intimal layer through diapedesis (Hanson and Libby, 2006). After a series of morphological changes, the leukocytes will ingest the oxidized LDLs and take on the role of a macrophage to develop into a foam cell (Libby, 2002).

The macrophages present in the intima will release growth factors which stimulate smooth muscle proliferation. As the smooth muscle replicates, the size of the lesion becomes larger which narrows the arterial lumen, a phenomenon known as atherosclerosis. The narrowing of the lumen diameter will alter or impede blood flow which will result in clinical manifestations (Libby, 2002).

1.5 C-Reactive Protein as a Marker of Inflammation

The presence of systemic inflammation, as indicated by levels of an acute phase protein and inflammatory marker known as C-reactive protein (CRP), is associated with the risk of atherosclerotic complications and can yield substantial clinical utility (Koenig et al., 1999; Libby et al., 2002). CRP was traditionally viewed as a plasma protein produced exclusively by hepatocytes; however, recent evidence has shown that arterial smooth muscle cells are able to synthesize CRP after stimulation of inflammatory cytokines (Yeh, 2005). CRP inhibits the activity of an enzyme known as nitric oxide synthase (eNOS) which is responsible for releasing a potent vasodilator, nitric oxide (NO). With a reduction in the bioavailability of NO, the artery has an impaired ability to vasodilate which increases the shear stress on the artery wall (Texeira et al., 2014). In fact, a nested-case control study including 28,263 post-menopausal women with a three-year follow-up period demonstrated the ability for CRP to independently predict the risk of a cardiovascular event (Ridker, 2003).

1.6 Traditional Cardiovascular Disease Risk Factors

Until recent years, CVD had been thought to be associated exclusively with adulthood and predicted by traditional risk factors identified by the various follow-up studies from the Framingham Heart Study (Kannel et al., 1961; Truett et al., 1968; Kannel et al., 1976; Wilson et al., 1998). A risk factor is described as

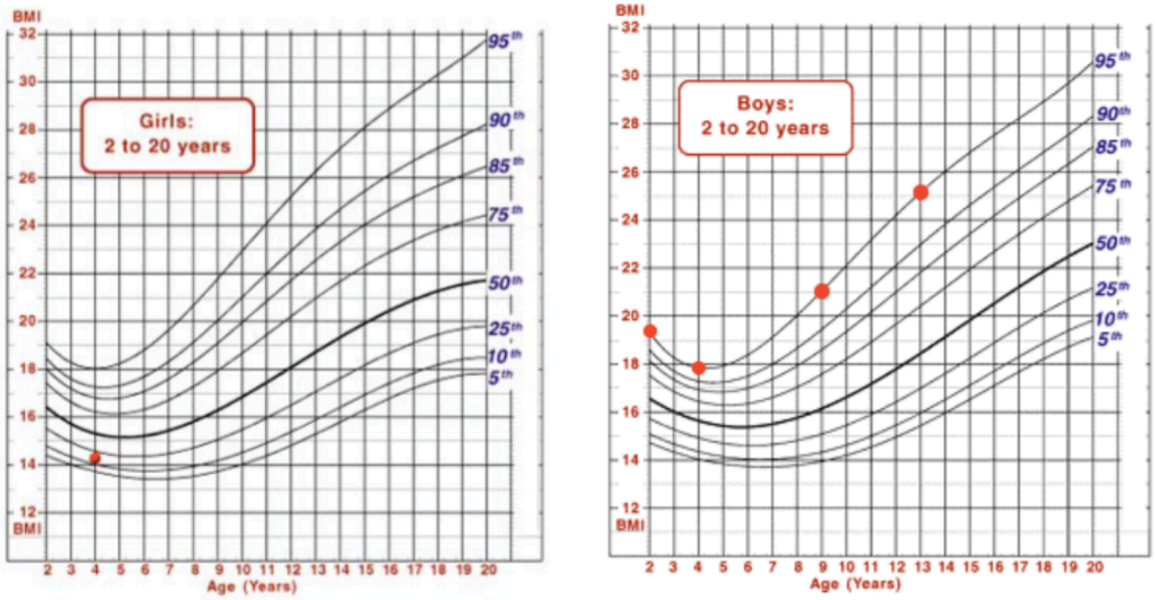
any characteristic that increases the risk for development of CVD (Gordon & Kannel, 1982) and includes age, family history of CVD, BMI, blood lipids, cigarette smoking and systolic and diastolic blood pressure. The modifiable risk factors to be included in this study include elevated BMI, low-density lipoprotein cholesterol (LDL-cholesterol), triglycerides and systolic and diastolic blood pressures as these are the risk factors that are likely most applicable to pediatric populations.

1.6.1 Body mass index

BMI is a weight-to-height ratio that is used for weight categories and can be used as an indicator of overall adiposity. It has been reported that overweight children have a greater chance of presenting with elevated cardiovascular risk factors such as high LDL-cholesterol, dyslipidemia and hypertension when compared to healthy controls (Freedman et al., 1999; Katzmarzyk et al., 2003). Furthermore, evidence suggests that overweight or obese children are likely to present as overweight or obese adults (Pietiläinen et al., 2001 & Srinivasan et al., 1996) and that childhood obesity initiates the metabolic pathways for cardiovascular disease in adulthood (Tounian et al., 2001). A follow-up study to the Atherosclerosis Risk in Young Adults (ARYA) study revealed that children with the largest BMI in young adulthood subsequently demonstrated the largest increase in carotid artery intima media thickness (Oren et al., 2003), highlighting

the link with obesity and structural changes in the arterial wall. In addition, structural changes in the artery have been also associated with high BMI as demonstrated by increased arterial stiffness and reduced reactivity of the brachial artery in obese children ranging from 2 to 15 years of age (Tounian et al., 2001).

Figure 1. *(A) BMI-for-age percentile curves for girls aged 2-20 years. Age (years) on the x-axis and BMI (kg/m^2) on the y-axis. (B) BMI-for-age percentile curves for boys aged 2-20 years. Age (years) on the x-axis and BMI kg/m^2) on the y-axis. (Centers for Disease and Control)*



The use and application of normative data for BMI in children and adolescents is more involved than the application of standard cutoff points that are commonly used in adult populations. Due to the disparity in size and growth rates

during childhood and adolescence (Sonksen, Gray, & Hickman, 1994), the Centers for Disease Control and Prevention (CDC) Growth Charts were created which contain BMI-for-age percentile curves for both girls and boys aged 2-20 years (Figure 1). Children in the in the 85th to less than the 95th percentile range are considered to be overweight and children at or above the 95th percentile are classified as obese (Kuczmarski et al., 2002).

1.6.2 Dyslipidemia

Cholesterol is a waxy lipid that is derived from liver synthesis and consumed through dietary intake (Freeman et al., 2005). Cholesterol is a ubiquitous compound that is present in all cell membranes and serves as the primary substance from which all steroid hormones are derived (Ronzie et al., 2003). The lipid structure of cholesterol makes it insoluble in water and therefore must be combined with specific protein carriers, known as lipoproteins, to be transported in the blood (Ronzie et al., 2003). Total blood cholesterol is composed primarily of the cholesterol in high-density lipoproteins (HDL cholesterol) and in LDL with the latter containing the majority of circulating cholesterol (Lewington et al., 2007). LDLs are responsible for carrying cholesterol from the liver to various tissues throughout the body (Freeman et al., 2005) and high levels of LDL-cholesterol have been demonstrated to be a considerable risk factor for cardiovascular disease (Bachorik & Ross, 1995; Nordestgaard et al., 2010). High

levels of circulating LDLs promote the adhesion of monocytes to the endothelial layer (Steinberg and Witzym, 1990). Once bound, these monocytes are able to penetrate into the intimal layer and recruit LDL through chemoattractant properties. The endothelium has the ability to oxidatively modify LDLs which is an important initiating factor of atherosclerosis in adults (Steinbrecher et al., 1984; Steinberg and Witzym, 1990). In fact, oxidized LDL has been shown to reduce the vasodilatory capacity of the endothelium in isolated arterial segments (Simon, Cunningham, & Cohen, 1990). Additionally, LDL has been shown to have the highest correlation to carotid artery intima-media thickness, a surrogate marker for preclinical atherosclerosis (Raitakari et al., 2003), when compared to other traditional risk factors such as BMI and systolic blood pressure (Li et al., 2003).

The 2007-2009 Canadian Health Measures Survey provided normative reference values for blood lipids in children. According to the values, healthy blood lipid profiles would contain total cholesterol <4.5 mmol/L, LDL cholesterol < 3.4 mmol/L, and HDL cholesterol > 1.3 mmol/L (Canadian Health Measures Survey, 2010). Since the publication of these normative values, new clinical data had emerged to support the revision of some of these guidelines, specifically lowering the LDL cholesterol target value to < 2.0 mmol/L for individuals who are deemed high risk (McPherson et al., 2006).

Triglycerides are esters formed by glycerol and three fatty acid chains which constitute as the major form of fats in the human body. These molecules are transported in very low-density lipoproteins (VLDLs) and chylomicrons (Sarwar et al., 2007) and serve as a potent energy provider; however, high plasma triglyceride concentrations are associated with a greater risk for CVD (Cullen, 2000). In fact, univariate relative risk estimates suggest a 1 mmol/L increase in triglyceride is associated with a 32% increase in CVD risk in men and a 76% increase in risk for women (Austin, Hokanson, & Edwards, 1998). These risks, however, were marginally attenuated when controlling for HDL, reducing the disease risk to 14 and 37% for men and women, respectively (Austin, Hokanson and Edwards, 1998). Despite this finding, a multivariate analysis from an 8-year follow up study found hypertriglyceridemia to be an independent risk factor for major coronary events after adjustment for HDL and LDL cholesterol, age and BMI (Assmann, Schulte, & von Eckardstein, 1996). Although these studies later received criticism for the lack of consideration for and control of within-day variability in triglyceride levels, Sarwar and colleagues (2007) have demonstrated a moderately high reliability of triglyceride levels over time suggesting that the criticism holds little strength.

Similar to cholesterol cutoffs, the Canadian Health Measures Survey also published data pertaining to target triglyceride levels in children. These data recommend that triglyceride levels are < 1.7 mmol/L in order to obtain a healthy

blood lipid profile (Canadian Health Measures Survey, 2010).

1.6.3 Blood pressure

Blood pressure refers to the force exerted on the vasculature by the circulating blood, measured in millimeters of mercury (mmHg), and is assessed in two phases of the cardiac cycle. Systolic blood pressure (SBP) refers to the force exerted on the systemic arterial walls during left ventricular contraction and ejection of blood into the circulatory system and diastolic blood pressure (DBP) is the force exerted on the systemic arterial walls when the left ventricle is at rest (Vanputte et al., 2014). As the blood exerts a force on the arterial wall, there is a mechanical deformation of the inner layer of the artery, known as the endothelium. If SBP becomes too high, this force may result in damaged endothelial cells and will promote the development of atherosclerosis (Myolonna-Karayanni et al., 2006). In fact, research has demonstrated that high SBP accelerates atherogenesis and may impart a 2-3 fold increased risk for atherosclerotic CVD (Kannel, 1996). This is supported by a retrospective analysis of the Framingham Study which demonstrates that SBP is directly linked with incidence of coronary heart disease (Stokes III et al., 1989). Specifically, D'Agostino and colleagues (1991) calculated biennial age-adjusted rates of cardiovascular disease per 1000 individuals and found coronary disease risk ratios of 2.0 for men and 2.2 for women with hypertension and even larger peripheral

artery disease risk ratios of 2.0 and 3.7 for hypertensive men and women, respectively.

Normative reference values for SBP and DBP cutoff values have been published by the National Heart, Lung and Blood Institute for children ranging from 1 to 17 years. The BP reference data is categorized into percentiles based on the age, sex and height of the child (Ouspensky, 2004) (Appendix A). Children above the 95th percentile for their age group are considered to be hypertensive.

Often times, the presence of one of the traditional risk factors is accompanied by the presence of at least one other, if not all other traditional risk factors. When controlling for these, it is possible to have an attenuation in CVD risk, suggesting that the presence of one of these risk factors may not be sufficient (Kannel, 1996). In fact, there is evidence which demonstrates that a mild hypertensive patient, in the absence of any other traditional risk factors, is at no greater risk for coronary events than a seemingly healthy member of the population of a similar age (Anderson, Wilson, Odell, & Kannel, 1991). Fortunately, technological advancements enabled the foundation for implementing novel techniques to assess both structural and physiological components of the artery and identify emerging CVD risk factors such as carotid artery intima-media thickness (cIMT), arterial stiffness and endothelial function.

1.7 Emerging Cardiovascular Disease Risk Factors

The emerging cardiovascular risk factors prove to be advantageous in that they are assessed non-invasively and may be useful in the detection of early changes in the composition of the vascular wall (Vlahos et al., 2011). This early detection allows for the identification of subclinical vascular dysfunction before the occurrence of any cardiovascular events. Although CVD is typically a disease that begins to manifest in adulthood, there is compelling evidence to suggest that it begins to develop early in life, suggesting the emerging CVD risk indicators are highly valuable measures for pediatric populations.

1.7.1 Common carotid artery intima-media thickness

Atherosclerosis is prefaced by morphological changes in the arterial wall that are long detectable before any clinical manifestation (Theocharidou et al., 2014) . The initial stage of atherogenesis is characterized by hyperplasia which serves to increase the thickness of the inner two walls of the artery, the intima and media, respectively. With the use of high-resolution B-mode ultrasound, the intima-media boundary as seen in the common carotid artery in the neck can be quantified non-invasively and reported as the cIMT. An increase in cIMT is associated with vascular risk factors leading to stroke and myocardial infarction (Chambles et al., 1997; Hodis et al., 1998; Dijk et al., 2006) and indicates a more advanced presence of generalized atherosclerosis, including coronary artery disease (Dijk et al., 2006). The strength of the findings surrounding the

methodology of cIMT has been validated with comparisons to direct histological examination (Bots et al., 2002) making it an easily accessible and valid risk marker. The reliability of cIMT gas been assessed in children and adolescents through B-mode ultrasound and found a reliability coefficient of 0.04mm (Aggoun et al., 2000).

The wealth of research surrounding IMT has enabled normative values that classify CVD risk to be created for adults (Geroulakos et al., 1994); however, there has been little research conducted to propose defined cutoff values for children. Jourdan and colleagues (2005) aimed to address the paucity of normative data for IMT in children by measuring cIMT in 247 healthy Caucasian children ranging from 10-20 years. The results from this study found no differences between male and female participants across all ages which allowed for the results to be pooled for both sexes. cIMT was shown to have a slight increase with age, increasing from 0.38 to 0.40mm between the ages of 10 and 20 years (Jourdan et al., 2005). The findings from this study are in accordance with a previous study in 5-14 year old Japanese children which demonstrated a 9μm increase in cIMT per year (Ishizu et al., 2004). Together these results support the theory of arterial wall ageing in early adolescence and require a range of values for comparative data based on age. The cIMT values for healthy adolescents as described by Jourdan and colleagues (2005) will be used for this study and ranges

from 0.38 to 0.40mm with 0.47mm being reported as the 90th percentile (Jourdan et al., 2005).

1.7.2 Arterial stiffness

Mechanical properties of the vasculature can be assessed through measuring arterial stiffness, which can provide information about the composition of the arterial wall (Stephane Laurent et al., 2006). The mechanical properties of the artery inherently predict the ability of the artery to rapidly distend during cardiac contraction which is followed by rapid recoil during diastole (Dorbin, 1978). These viscoelastic properties are a key determinant in instantaneous arterial pressure. In fact, increased arterial stiffness results in an earlier return of the reflected wave from the periphery during late systole (Haller et al., 2004). The premature return of the reflected waveform will ensue an additive effect on the pulse pressure which subsequently increases systolic blood pressure (SBP) (Nicols & O'Rourke, 2005). A higher pulse pressure on the arterial wall will cause a greater workload for the left ventricle resulting in left ventricular hypertrophy (Mattace-Raso et al., 2006) which can become pathological with chronic exposure.

Pulse wave velocity (PWV) is an index that can be used to assess the speed at which a pulse wave travels through an artery or given segment of the arterial tree. As arteries stiffen, they lose their ability to cushion the pulse wave

which results in a decreased pulse transit time (Stephane Laurent et al., 2006). A pulse wave with a faster velocity is indicative of a stiffer artery, therefore this measure can be used as marker of vascular damage and a prognostic predictor (Yamashina et al., 2002). In fact, aortic PWV has been used as a measure of central arterial stiffness and has been shown to predict cardiovascular outcomes in patients with hypertension (Laurent et al., 2001; Laurent et al., 2003), diabetes (Cruickshank et al., 2002), end stage renal-disease (Blacher et al., 1999) and elderly hospitalized patients (Meaume et al., 2001).Additionally, a study including 1678 Danes (40-70 years) determined that aortic PWV had significant prognostic value of future CV events in the general Danish adult population (Hansen et al., 2006).

Local arterial stiffness of a specific artery can be measured through assessment of the arterial compliance and distensibility. A measure of the buffering capacity of an artery, compliance refers to the change in diameter per a given unit of pressure (Van Bortel, Kool & Struijker Boudier, 1995) and is an important determinant of afterload on the left ventricle (Levy and Safar, 1990). Distensibility is a measure of the relative change in diameter per a given unit of pressure (Van Bortel, Kool & Struijker Boudier, 1995) and is seen as a determinant of stress on the arterial wall. In fact, a decrease in distensibility is believed to increase the stress on the arterial wall and may lead to damage promoting the atherosclerotic process (Badimon, Badimon & Chesebro, 1992).

Although there are no established stiffness cutoff values for future CVD risk in children, there is substantial literature demonstrating increased arterial stiffness in a variety of pediatric populations predisposed to various traditional CVD risk factors (Tounian et al., 2001; Urbina et al., 2009). Specifically, a study including 48 obese children (mean age 12.6 years) and 27 healthy controls (mean age 12.0 years) demonstrated that obese children had reduced arterial compliance and distensibility (Tounian et al., 2001). Furthermore, Urbina and colleagues (2012) conducted a study to assess the relationship of high triglyceride to HDL cholesterol ratios (TG:HDL) on arterial stiffness which included 893 children and young adults (10-26 years) free of chronic disease or any medication affecting carbohydrate metabolism and non-pregnant females. The participants in this study were stratified into tertiles based on low, medium or high TG:HDL and the results reported higher PWV for those in the high TG:HDL group compared to the low TG:HDL group (Urbina et al., 2009).

1.7.3 Endothelial dysfunction

The endothelium is a single layer of cells that lines the lumen of the artery and is in direct contact with the blood. As blood flows through the artery, it exerts a translational force on the endothelial cells which stimulates the release of a potent endothelium-derived vasodilator known as nitric oxide (NO). When the endothelium becomes damaged, there is a reduction in the bioavailability of NO,

which may be subsequently accompanied by an increase in endothelial constricting factors such as endothelin-1 (ET-1) (Ciarla et al., 2001). Ultimately, the reduction in NO bioavailability results in an alteration in endothelial physiology and an impaired ability for arterial reactivity, a phenomenon termed endothelial dysfunction, and plays a key role in the development of atherosclerosis (Ross, 1999; Satija et al., 2014). Indeed, endothelial dysfunction has been shown to be an early event in atherogenesis as evidenced by its early presence in children and adults with traditional CVD risk factors before the formation of intimal plaque (Celermajer et al., 1992). The knowledge of early presence of endothelial function led researchers to explore the prognostic value of endothelial function in predicting future CV events in a number of adult populations (Brevetti et al., 2003; Heitzer et al., 2001; Noyan et al., 2003). Heitzer and colleagues (2001) prospectively studied 281 adult patients referred for a coronary artery disease assessment and found that the presence of endothelial dysfunction predicts the risk of cardiovascular events (Heitzer et al., 2001). A later study conducted by Brevetti and colleagues (2003) followed up these findings by including 131 adult patients with peripheral artery disease (PAD) (63.8 ± 9.5 years) and found endothelial dysfunction to be an independent predictor of future CVD risk in this population (Brevetti et al., 2003).

As a means to assess endothelial function, a non-invasive sonographic

technique was developed to evaluate flow-mediated dilation (FMD) in the brachial artery (Anderson & Mark, 1989). In principle, the FMD test involves a brief occlusion of blood flow through a peripheral limb conduit artery through the application of an occlusion cuff. Once the cuff is deflated, there is a rapid increase in blood flow through the artery which will stimulate the increase in blood flow. The transient release of vasodilators will be accompanied by vasodilation which can be imaged and quantified as an index of vasomotor function.

The rate and timing of growth of arteries differ between sexes and age groups (Nicola D. Hopkins et al., 2015) rendering it difficult to develop normative FMD values in children and adolescents. Jarvisalo and colleagues derived normal FMD values from 105 healthy children and determined endothelial dysfunction to be present when the total dilation response was below the 10^{th} percentile, corresponding to a cut off point for a peak FMD <3.3% (Järvisalo et al., 2004). The FMD test has been proven to be reliable in healthy adolescent boys aged 12-15 years with a CV of 5.1% for ratio-scaled FMD and 10.6% for allometrically scaled FMD (Bond, Williams & Barker, 2016).

1.8 Pathophysiology of Cardiovascular Disease

Endothelial dysfunction is an early event in the atherosclerotic process (Widmer & Lerman, 2914). When the endothelium becomes damaged, there is an impairment in vasodilation of the artery which will result in increased luminal

pressure and the stimulation of excessive collagen productions (Zieman, Melenovsky and Kass, 2005). The relative contribution of collagen and elastin in the arterial wall is typically held stabled; however, the molecular changes that manifest with the increased shear force on the arterial walls with endothelial dysfunction will increased the IMT (Zieman, Melenovsky & Kass, 2005). In fact, research has shown that the IMT can double or even sometimes triple in thickness between the ages of 20 to 90 years (O'Leary et al., 1999). If the exposure to the hypertensive and/or inflammatory milieu remains, the later stages of cardiovascular disease pathophysiology will result in abnormal accumulation of collagen and diminished elastin in the arterial walls which contributes to arterial stiffness (Johnson et al., 2001).

1.9 Chronic Inflammatory Conditions

There is evidence to suggest an increase in the prevalence of traditional and emerging CVD risk factors in children with a chronic inflammatory condition (Kavey et al., 2006) although these findings are largely conflicted (Figure 2). It has been suggested that this increase in markers of vascular damage in children with a chronic inflammatory condition is due to the common disease aetiology pathways between the inflammatory and immune mechanisms of atherosclerosis and chronic inflammatory disease (Vlahos et al., 2011).

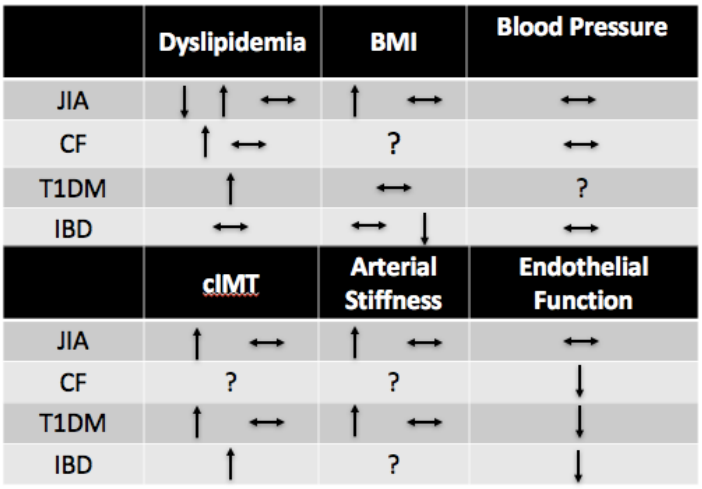


Figure 2. A summary of the current literature investigating traditional (top) and emerging (bottom) CVD risk factors in children with JIA, CF, T1DM and IBD. Down arrows = decrease in risk factors, up arrows = increase in risk factors, two-way arrows = no differences in risk factors.

1.9.1. Juvenile Idiopathic Arthritis (JIA)

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases in childhood and requires a diagnosis prior to the age of 16 years (Prakken et al., 2011). JIA is a heterogeneous group of conditions characterized by inflammation of the joints of varying severity. The International League of Associations for Rheumatology (ILAR) classification system categorizes JIA into seven subtypes of disease although the patients may be divided into larger groups of oligoarticular and polyarticular JIA depending on the number of joints involved (Weiss & Ilowite, 2007). Ranging from the least severe to the most involved, the subtypes include oligoarticular JIA, polyarticular JIA and systemic JIA. The

origin of JIA is unknown although it is believed that both genetic and environmental factors play a role (Ravelli & Martini, 2007). To exacerbate the complexity of this disease, it is possible for afflicted children to enter remission, however, over 50% of patients have persistent symptoms after eight years of disease onset (Alberdi-Saugstrup et al., 2017; Nordal et al., 2011). Ou and colleagues (2002) assessed serum inflammatory markers in 14 children with JIA at two time points, including one measure during active disease and one during inactive disease, and found higher CRP levels during active (36.6 ± 37.2 mg/L) compared to inactive disease (5.9 ± 2.1 mg/L) (Ou et al., 2002). The researchers characterized active disease by effusion, swelling, or the presentation of two of the following symptoms: impaired joint range of motion, tenderness or pain associated with movement and increased temperature of one or more of the involved joints whereas inactive disease included the absence of any of these symptoms (Ou et al., 2002). Although the JIA patients had significantly reduced CRP levels during their inactive phase, it should be noted that the mean CRP levels for this group is above the high risk CRP cut-off values of 3 mg/L (Musunuru et al., 2008). Sustained inflammation is known to accelerate atherosclerosis which puts individuals with JIA at an increased risk for CVD (Coulson et al., 2013).

1.9.2. JIA and Traditional Risk Factors

The lipid profiles of patients with JIA demonstrates the greatest disparity between studies (Bakkaloglu et al., 1996; Ilowite et al., 1989; Tselepis et al 1999; Marangoni et al., 2011). An early study exploring dyslipidemia in this population failed to demonstrate any significant differences in the lipid profiles of patients with JIA compared to healthy controls except for reduced levels of LDLs (Bakkaloglu et al., 1996). This finding is contrasted by a report of decreased levels of HDL and increased levels of VLDLs and triglycerides in children with JIA (Ilowite et al,, 1989), primarily observed in those with systemic JIA or high disease activity. Furthermore, in 1999, Tselepis and colleagues found reduced levels of HDL and increased levels of triglycerides in patients with active JIA but not in those with inactive JIA, suggesting a possible link between disease activity and lipid profiles (Tselepis et al., 1999). More recent work has demonstrated a reduction in HDL levels in patients with JIA but no significant correlation to disease activity or duration (Marangoni et al., 2011). The authors speculated that the complexity and variability of this disease may be in part responsible for the observed variability in lipid profiles in these patients or could be possibly influenced by some of the prescribed medications (Marangoni et al., 2011).

Previous research pertaining to obesity and/or BMI in children with JIA has yet to demonstrate any consistent findings. Despite their reduced levels of physical activity (Bohr et al., 2015) and use of steroid therapies, patients with JIA

have reported low BMIs believed to be due to nutritional impairment (Cleary et al., 2004). In fact, a more recent study including 154 American children with JIA found that only 18% of these patients were obese which was found to be a very similar obesity rate seen in the general population of U.S. children at the time (Pelajo, Lopez-Benitez, & Miller, 2012). Contrary to these findings, a study conducted in 58 Moroccan children with JIA reported that 41% of their participants had a BMI classification of overweight and 22% had a BMI classification of obese (Amine et al., 2011). Additionally, Caetano and colleagues (2012) examined the relationship of obesity in female children and adolescents with JIA and found that they had higher mean Z-BMI scores, total body fat percentage and truncal fat when compared to healthy controls. The reports suggesting increased rates of adiposity have been conducted on very specific populations which may not be generalizable. Nonetheless, the literature examining obesity in this population leaves an unclear knowledge gap.

There has been consistency regarding the relationship of both SBP and DBP in children with JIA amongst the available literature. Almost all studies comparing children with JIA to healthy controls who report SBP and DBP found no differences in these two measures (Ilisson et al., 2015; Satija et al., 2014; Sozeri et al., 2016; Vlahos et al., 2011) Interestingly, this relationship has proven true when examining children with a variety of subtypes of JIA (Illison et al.,

2015; Satija et al., 2014; Vlahos et al., 2011) and systemic JIA exclusively (Sozeri et al., 2016). The results from these findings support the theory that children with JIA, regardless of their subtype of disease, may experience hypertension at rates that are similar to their healthy counterparts.

1.9.3. Emerging CVD Risk Factors and JIA

The increased levels of CRP noted in patients with JIA has been positively associated with increased cIMT (Pietrewicz & Urban, 2007; Vlahos et al., 2011; Satija et al., 2014). Pietrewicz and Urban (2007) demonstrated an increased cIMT in pediatric populations with both polyarticular and oligoarticular JIA when compared to healthy, age-matched controls. However, this observation was later contrasted by Vlahos and colleagues (2011) who found increased cIMT in patients with systemic JIA but no significant differences between those with polyarticular JIA or oligoarticular JIA and healthy controls. Based on these findings, it would be plausible to deduce a potential relationship between cIMT and disease severity; however, there were a number of confounding variables. Further analysis revealed significant differences in BMI, corticosteroid use and DBP among the three subtypes of disease in the study by Vlahos et al. (Vlahos et al., 2011). In addition, there have been more recent studies demonstrating no significant differences in cIMT for any of the three subtypes compared to healthy controls (Satija et al., 2014; Evenson et al., 2016). The conflicting literature pertaining to the

relationship between cIMT and JIA therefore requires further investigation.

In conjunction with increased cIMT, Sozeri and colleagues (2016) demonstrated an increased arterial stiffness throughout the arterial tree in 33 children with systemic JIA as indicated by higher PWV (Sozeri et al., 2016). The findings from this study are in contrast to an earlier study by Vlahos and colleagues who assessed 30 children diagnosed with either oligoarticular, polyarticular or systemic JIA (7-18 years) and found no differences in PWV when compared to healthy controls (Vlahos et al., 2011). When taking into account confounding variables, a significant relationship was found between arterial stiffness and corticosteroid use (Vlahos et al., 2011) as well as disease duration (Sozeri et al., 2016) which could partially explain the apparently disparate results in these studies.

Local arterial stiffness, as indicated by common carotid artery compliance and distensibility, has also been shown to be elevated in children with JIA in comparison to healthy controls. In a group of 31 children with active JIA, common carotid artery cross-sectional compliance was significantly impaired in patients with JIA compared to controls by 20% (Satija et al., 2014). Similarly, cross-sectional distensibility was also found to be lower by 18% (Satija et al., 2014); however, studies examining the relationship of local stiffness in the carotid artery are sparse. These reports suggest that further examinations of these

relationships are warranted to characterize the relationship.

Patients with active JIA have demonstrated elevated levels of soluble intercellular adhesion molecules (sICAM-1), a pro-inflammatory molecule associated with endothelial activation and vascular dysfunction (De Benedetti et al., 2000). A cross-sectional study including 30 children and adolescents with JIA reported a 30% reduction in FMD compared to healthy controls although the decreased FMD response was attenuated once differences in ICAM-1 were adjusted for. (Vlahos et al., 2011). When the 30 JIA patients were divided among their disease subtypes, the researchers found no differences in FMD between the different subtypes.

Contrary to these results, Satija et al. (2014) performed similar vascular analyses in 31 patients with JIA and found no significant differences in FMD between patients and controls. There were, however, limitations to this design as the authors failed to report whether their values were reported as relative or absolute FMD. This becomes an important factor to consider as there were differences in the resting baseline diameters of the brachial artery. Superficially, children with JIA had smaller resting diameters than the healthy controls. With a larger resting diameter, there is less ability for the artery to expand during reactive hyperemia (Corretti et al., 2002), demonstrating components of a ceiling effect. On the other hand, smaller arteries will have a greater capacity to vasodilate and

will exhibit a larger relative change (Celarmarjer et al., 1992). Without controlling for baseline diameter and reporting the FMD values as relative change, these small differences in baseline diameter could have influenced the results of this study.

1.9.4. Cystic Fibrosis (CF)

Cystic fibrosis is a fatal genetic disorder that is characterized by abnormally thick mucus in various exocrine glands, specifically the pancreas, and the intrapulmonary surface. The increase in mucus on the airway surface results in impaired mucociliary clearance (Elizur, Cannon, & Ferkol, 2008) and a buildup of bacteria which promotes the vulnerability of chronic lung infections (Davis, 2006). The presence of an infection in the lung will then initiate and sustain the inflammatory response in the airways (Laval, Ralhan, & Hartl, 2016) resulting in an amplification of the inflammatory load associated with this condition. Bronchoalveolar lavage fluids of pediatric populations with CF have revealed increased neutrophils and interleukin-8 (IL-8) when compared to healthy children of similar age and children with other chronic respiratory conditions (Gibson et al., 1984). As CF progresses, the local inflammatory response in the lungs has been shown to be associated with a systemic inflammatory response (Elizur, Cannon & Ferkul, 2008). In fact, it has been reported that adult patients with CF have significantly higher levels of CRP than their healthy counterparts

(Carpagnano et al., 2003), suggesting a greater risk for low-grade inflammatory conditions such as atherosclerosis (Alberdi-Saugstrup et al., 2017). Despite strong evidence demonstrating increased levels of inflammation and oxidative stress (Reverri et al., 2014), there has been little research associating CF with an increased incidence of CVD, in part due to the shortened life expectancy (Skolnik et al., 2016).

1.9.5. Traditional CVD Risk Factors and CF

There have been few studies reporting data on the prevalence of traditional CVD risk factors in both adult and pediatric patients with CF. A retrospective analysis from a routine lung transplant cardiovascular screening process included 330 adults with CF from the years 1996 to 2016. The results revealed that 78% these patients possessed reduced HDL levels and the remaining 22% had high total cholesterol while none of the patients showed abnormalities in triglycerides or LDL levels (Skolnik et al., 2016). Additionally, none of these patients had a reported history of hypertension. From these results, it would appear as though individuals with CF are not at an increased risk for CVD. Future research with stronger methodological design could help explore this relationship further.

There is lack a lack of literature that provides a direct comparison of BMI in children with CF to healthy age-and-sex matched controls. Despite this, it has been well established that children with CF have impaired somatic growth as

evidenced by frequently being below the growth standard for height and weight (Parsons et al., 1993; Henderson et al., 1999). The reduced weight gain seen in this population is believed to be partly caused by malnutrition (Henderson et al., 1999) which has implications for poor survival in this population (Corey et al., 1988). Indeed a study including 50 children with CF (7.7-16.7 years) showed a positive correlation between BMI and lung function (Pedreira et al., 2005).

1.9.6. Emerging CVD Risk Factors and CF

The prevalence of emerging CVD risk factors in patients with CF has been largely unexplored. A preliminary report suggests that pediatric patients with CF may experience endothelial dysfunction (Poore et al., 2013). A cross-sectional report with 30 children (15 diagnosed with CF and 15 healthy controls) aged 7 to 18 years demonstrated that children with CF have a significantly reduced absolute FMD while baseline and peak diameters were not different. Shear rate was shown to be similar between patient and controls; however, FMD normalized for shear rate was significantly lower in patients with CF than in healthy controls. Although these preliminary findings seem promising, it is well documented that the severity of CF gets worse with age and a sub-analysis adjusting for age may have been useful to help classify the risk for this population. Nonetheless, the well-established link between inflammation and atherosclerosis (Libby, 2002) warrants further investigation of children with CF to elucidate the relationship between risk

for future CVD events and this disease.

1.9.7. Type I Diabetes Mellitus (T1DM)

Type I diabetes mellitus (T1DM) is a T-cell mediated autoimmune disease in which the target is the pancreatic beta cells. In T1DM secretion of insulin is impaired and hyperglycemia results (Rother, 2014). Adults with T1DM have increased levels of inflammation, as indicated by significantly higher levels of plasma CRP (Ciarla et al., 2001; Schram et al., 2003; Aljabri et al., 2010). Indeed, adult T1DM patients demonstrated a 42% increase in plasma high sensitive CRP (hsCRP) when compared to healthy, age-, sex-, BMI- and ethnicity matched controls (Aljabri et al., 2010). Not surprisingly, individuals with type I diabetes have been reported to have between a 2 to 4-fold increased risk for developing atherosclerotic disease (Järvisalo et al., 2004). Most interestingly, this increased CVD risk cannot be adequately explained by traditional CVD risk factors alone (Pyorala, Laakso &Uusitupa, 1987), which indicates emerging CVD risk factors may be important assessment tools.

1.9.8. T1DM and traditional CVD risk factors

Plasma hemoglobin 1Ac (HbA1c) is a marker of mean ambient blood glucose over a 2-3 month period which is used to characterize abnormal blood glucose levels (O'Sullivan et al., 2006). Elevated HbA1C has been associated

with vascular complications in type 1 diabetic patients (Nabulsi et al., 1993). An early study examining plasma lipid levels and hyperglycemia revealed a pattern in which total cholesterol, LDL levels and triglycerides increased significantly with a poor control of the diabetic condition, indicated by levels of HbA1c (Sosenko et al., 1980). The children with diabetes were divided into three groups categorized the participants into low (<13%), medium (13 to 15%) and high (>15%) levels of HbA1c which revealed that the participants in the medium and high categories had significantly greater lipid levels, except for HDL, when compared to healthy, sibling controls. These findings support the theory that altered lipid profiles in T1DM may be related to the hyperglycemic state. Since this time, there have been target levels for both HbA1c and lipid levels established by the American Diabetes Association (ADA) (Silverstein et al., 2005) as well as the International Society for Pediatric and Adolescent Diabetes (ISPAD) (Donaghue et al., 2007) to help with the prevention and management of this disease. A comprehensive cohort study was conducted in order to assess the proportion of children with T1DM who were receiving care from a pediatric endocrinologist and met these target levels (Wood et al., 2013). Of the 13, 226 participants in which HbA1c was collected, only 32% met the target for ADA guidelines while 25% of the children met the target for ISPAD, suggesting a high proportion of these children were in a hyperglycemic state. Despite these increased HbA1c levels, majority of the children met the target levels for both LDL levels (65.5%) and triglycerides

(91.5%). These results conflict with the earlier work done by Sosenko and colleagues (1980), although it should be noted that the average levels of HbA1c in the latter study ranged from 8.2 to 8.8% for various age categories which would categorize these children in the low HbA1c category used previously. The lower levels of Hb1Ac overall in 2013 could be reflective of better disease management or perhaps differential techniques for measuring HbA1c over the last few decades.

Trends have demonstrated an increase in the proportion of overweight and obese adult patients with T1DM (Miller & Kelsey, 2011). It is proposed that this shift can be largely contributed by epidemiological shifts in society as a whole, more frequent caloric intake to battle symptoms of hypoglycemia, and intensive diabetes mellitus therapy (de Ferranti et al., 2014). Despite the link between childhood and adult obesity, there has been little research to explore the trends of obesity in children with a diagnosis of T1DM.

There is evidence to suggest that higher infantile weight is associated with a greater risk for developing T1DM later in childhood (Hypponen et al., 2000). Higher infantile weights may predispose patients with T1DM to have higher BMIs later in life when compared to their healthy counterparts. This thought, however, has had lacking support in the current evidence. In fact, studies examining both traditional and emerging CVD risk factors have demonstrated no differences in BMI between children with T1DM and healthy controls (Emre et

al., 2006; Järvisalo et al., 2002; Jarvisalo et al., 2004; Pozza et al., 2007).

Reports have demonstrated that adult patients with T1DM have a similar prevalence of hypertension as the general population (Sowers et al., 2001; Lurbe et al., 2002). When examining studies reporting SBP and DBP in pediatric patients with T1DM, it would appear that there are no differences in these measures when compared to BP values of healthy controls (Emre et al., 2006; Järvisalo et al., 2004; Pozza et al., 2007; Stakos et al., 2005). A recent study including 13, 226 children from the T1D Exchange Registry Clinic found that the BP guidelines, as outlined by ADA and ISPAD, were only met by 78% of the sample (Wood et al., 2013). The findings from this help indicate that there may be a higher proportion of pediatric T1DM patients not meeting the guidelines than originally thought.

1.9.9. Emerging Risk Factors in T1DM

The predominant finding in the literature is that children with T1DM have a greater cIMT than healthy controls (Jarvisalo et al., 2004; Emre et al., 2006; Stakos et al., 2005; Bayir et al., 2014) although there are a number of studies that have found cIMT levels to be similar between groups (Parikh et al., 2000; Yavuz et al., 2002; Singh et al., 2003). The results from early work by Yamasaki and colleagues in 1994 suggest a possible link between age and cIMT in T1DM patients. The researchers found similar cIMT values in children with T1DM aged

4-9 years (n=23) and significantly increased cIMT in patients aged 10-19 years (n=68); however, the sample size was quite small in the younger group which could introduce a greater possibility for a type 2 statistical error.

The conflicting results could be due to the varied techniques used to assess cIMT. Some studies report manually tracing the IMT while others report using automatic contour analyzing software. In addition, some study designs employed high-resolution ultrasound systems with probes up to 12 MHZ while others reported the use of probes of medium-resolution of 8MHZ. In addition, it has been suggested that endothelial dysfunction in children with T1DM may predispose these children to the development of elevated cIMT (Jarvisalo et al., 2004). A disturbance of normal, laminar shear stress may interfere with the production of endothelium-derived nitric oxide (NO). Chronic elevations in shear stress and inflammation may stimulate changes in signaling that result in altered expression of blood vessel wall components and thereby result in altered vascular structure in the form of increased artery wall thickness (Davignon et al., 2004). It is theorized that this process requires a considerable exposure to the diabetic milieu before cIMT becomes manifest (Singh, Groehn, & Kazmers, 2003) and may help explain why some studies demonstrate differences while others do not. The variability surrounding cIMT and children with T1DM warrants further systematic investigation.

In contrast to the prevalence of literature investigating cIMT in pediatric patients with T1DM, arterial stiffness has received very little attention. Haller and colleagues were the first research group to assess arterial stiffness in 2004 and examined the augmentation index (AI) in children ranging from 10-18 years of age and found higher mean AI in patients with T1DM when compared to control subjects. AI measures the relative contribution of the reflected waveform to the arterial pressure waveform, a parameter that is largely dependent on the stiffness of arteries in the systemic tree (Haller et al., 2004). As arteries increase in stiffness, the contribution of the reflected waveform increases which causes the AI to consequently become larger. The finding of higher AI in children with T1DM was supported by a more recent study demonstrating a significantly elevated mean AI in children with T1DM ranging from 4.7 to 18.6 years (Heilman et al., 2009). Most interestingly, Heilman and colleagues added a measurement of central arterial stiffness by assessing aortic PWV and found no significant differences between the two groups. These results seemed to initially suggest that early atherosclerotic changes are more likely to occur in peripheral than in central arteries; however, a more recent study assessing the compliance of the common carotid artery in the neck reported significantly reduced arterial compliance and an increased stiffness index in children with T1DM (Bayir et al., 2014).

Early studies assessing endothelial function in pediatric patients with T1DM have primarily focused on adolescents and have revealed that these

patients have a reduced FMD response when compared to their healthy counterparts (Donaghue et al., 1997; Wiltshire et al., 2002; Singh, Groehn & Kazmers, 2003). These findings led researchers to explore this relationship in even younger patients with T1DM. Jarvisalo and colleagues conducted a cross-sectional study in 2004 that included children ranging from 7-14 years of age who had a shorter disease duration and were free of any diabetic complications. The results from this study revealed that children with T1DM have a reduced peak and total FMD response. Strengthening these findings, it was also found that there were no differences in baseline artery diameter and shear rate during reactive hyperemia between patients with T1DM and healthy controls (Jarvisalo et al., 2004).

1.9.10. Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is an umbrella term that is comprised of two disorders known as ulcerative colitis (UC) and Crohn's disease (CD) (Hanauer, 2006). Affecting any part of the gastrointestinal tract, IBD is characterized by chronic and uncontrolled inflammation of the intestinal mucosa (Papadakis & Targan, 2000) which results in architectural distortion. Patients with IBD have an inability to down-regulate the inflammatory response, making chronic inflammation a key component and diagnostic tool (Hanauer, 2006). Indeed, a study conducted in 91 children (3-18 years) referred for an endoscopic

assessment by consultant pediatricians reported that simple routine blood tests, specifically including levels of CRP, are highly useful in diagnosing IBD when combined with an endoscopic assessment (Beattie, Walker-Smith & Murch, 1995). In this sample, 100% of patients with CD and 60% of patients with UC had significantly elevated CRP, thereby supporting the theory of systemic inflammation and increased risk for cardiovascular events for these populations (Ridker, 2003; Yarur et al., 2011).

1.8.11. IBD and traditional CVD risk factors

Traditional CVD risk factors have been largely unexplored in children with IBD; however, the current evidence fails to show a prevalence of risk factors in this population. In fact, when examining lipid profiles in children with IBD, Kim et al. (2014) reported significantly higher levels of total cholesterol and levels of LDL in healthy controls compared to children with IBD while levels of HDL and triglycerides were not different (Kim et al, 2014).

Blood pressure values have been evaluated in three studies all of which found no differences in SBP between pediatric patients with IBD and healthy controls (Aloi et al., 2012; Kim, Jang & Lee, 2014; Lurz et al., 2017). Although this pattern was similarly followed for DBP, there was one study which demonstrated a higher diastolic blood pressure in patients with IBD (Aloi et al., 2012).

The trend observed in the literature regarding increased BMI for those at an increased risk for CVD is directly opposite to what is seen in pediatric patients with IBD. Indeed, the studies reporting BMI in children with IBD have shown no differences (Lurz et al., 2017) or reduced BMI scores (Aloi et al., 2012; Kim, Jang & Lee, 2014) when compared to healthy controls. These findings are suggestive of a lower BMI; however, this finding could possibly be biased by the reduced ability for nutrient absorption in this population (M. O'Sullivan & O'Morain, 2006).

The paucity of research linking traditional CVD risk factors to IBD seems discouraging, although it has been suggested that using a prediction scoring system using only traditional CVD risk factors may underestimate the risk of future CVD events in patients with chronic systemic inflammatory disease (Wilson, 2008). Including biomarkers of inflammation and emerging CVD risk factors may will add predictive value for future CV events (Vasan et al., 2003).

1.9.12. Emerging CVD Risk Factors in Children with IBD

Not unlike the previous inflammatory conditions discussed, the literature pertaining to the emerging cardiovascular risk indicators in patients with IBD have shown conflicting data; however, the majority of the research previously conducted has been exclusive to adults. There are a number of studies reporting an increased cIMT in adult patients with IBD ranging from 20-45 years of age

(Kayahan et al., 2012; Ozturk et al., 2015) which helps implicate IBD as a factor that accelerates atherosclerosis. On the contrary, other studies have found no differences between adult patients and healthy controls which draws into question any potential association between IBD and atherogenesis (Kim, Jan & Lee,2014; Broide et al., 2011).

The limited literature pertaining to the pediatric population with IBD has shown a similar pattern to the findings reported in adult patients. A cross-sectional study conducted in a sample of patients with IBD (n=42; n=27 for CD, n=25 for UC) with a mean age of 15.2 years reported elevated cIMT in those with IBD compared to controls (Aloi et al., 2012). Further analysis revealed that there were no differences in cIMT values between UC and CD although univariate analysis revealed a stronger correlation between disease activity levels in CD than in UC. Interestingly, these findings were partially contrasted by a later report by Aloi and colleagues in 2015 which cited a higher mean cIMT in children with IBD which was not statistically different from healthy controls. However, in the same study greater abdominal aortic IMT was observed in the children with IBD (Aloi et al., 2015). Research suggests that abdominal aortic IMT is a better measure of early vascular disease as it is the location where fatty plaques are most likely to develop in young patients (McGill et al., 2000). The latter study included a sample that was younger in age (5 to 17 years, mean 11.1 years) which may explain the

different findings, with significance being exhibited in a measure pertaining to earlier change in an area adjacent to the site of inflammation.

The examination of arterial stiffness in pediatric patients with IBD is an area that has been largely void. A pilot study recently published including 25 children diagnosed with IBD (mean age14.1 years) reported similar carotid to femoral PWV values compared to published reference values (Lurz et al., 2017). Although useful to initiate interest in this area, this study presents some limitations. Firstly, it should be noted that there was no healthy control group to make a direct comparison to. In addition, nearly 70% of these patients were in clinical remission while the remaining participants were said to have mild disease activity. It should also be noted that 48% of children in this study were using anti-inflammatory medication with anti- tumor necrosis factor (TNFα) agents which have shown to have a positive influence on arterial stiffness in adult patients with IBD. The combination of the high proportion of participants in clinical remission and on anti- TNFα agents could have biased the results in terms of having PWV values in the normal, healthy range.

Decreased endothelial function has been consistently reported in adult patients with IBD when compared to healthy controls (Kayahan et al., 2012; (Ozturk et al., 2015) and there are similar preliminary findings related to endothelial function in pediatric patients with IBD (Aloi et al., 2012). A cross

sectional analysis of 42 children with IBD (27 with CD and 25 with UC) reported that %FMD was significantly reduced in both UC and CD when compared to 31 healthy controls (Aloi et al., 2012). Disease severity was assessed using the Pediatric Crohn's Disease Activity Index (PCDAI), Pediatric Ulcerative Colitis Activity Index (PUCA), disease duration and number of hospitalizations. A subgroup analysis revealed that the magnitude of the reduction in FMD was increased for those with severe CD compared with mild CD (Aloi et al., 2012), suggesting a possible link between FMD and disease severity. The relatively small sample of healthy controls in this study was a limiting factor. Having a repeated measure with a similar protocol and larger sample would help validate the preliminary evidence suggesting the presence of subclinical, premature atherosclerosis in this population.

1.10. Purpose

The previous literature regarding traditional and emerging cardiovascular disease risk factors in children with chronic inflammatory conditions has produced conflicting results. A combination of small sample sizes and varying measurement techniques may be responsible for the lack of sound evidence upon which to draw strong conclusions about causal relationships. Further examination of both emerging CVD risk markers and traditional CVD risk factors in children with inflammatory conditions would enable researchers to characterize the CVD

risk factors and identify useful targets for interventions and more accurate CVD risk monitoring in these populations. As of yet, there have been no studies that have simultaneously examined both traditional and emerging CVD risk factors in a cohort of children with a range of inflammatory conditions which could facilitate the identification of common disease pathways and future intervention targets. The purpose of this study is to investigate the traditional and emerging CVD risk factors in children with a range of chronic inflammatory conditions and to determine if these CVD risk factors differ from healthy, aged and sex-matched controls. The primary goal of this study is to determine if there are differences in cIMT, arterial stiffness and endothelial function between children with an inflammatory condition and healthy controls. The secondary goal is to determine if the children with inflammatory disease differ in inflammatory levels, BP, BMI, or blood lipids compared to healthy controls. Specifically, our primary outcome will be endothelial function due to the early influence a deregulatory endothelium can have in cardiovascular pathophysiology.

1.11. Hypothesis

We hypothesize that children with chronic inflammatory conditions will have increased chronic inflammation evident by elevations in markers of systemic inflammation and will also have increases in traditional (total cholesterol, LDL-cholesterol, triglycerides, SBP, DBP and BMI), and emerging (cIMT, arterial

stiffness, and endothelial dysfunction) CVD risk factors compared to healthy controls age-and-sex matched controls.

CHAPTER 2 - METHODOLOGY

2.1 Participants

Twenty-one participants with a chronic inflammatory condition (CIC) (12.5 ± 2.3 years) and nine healthy, age- and sex-matched controls (CON) (13.4 ± 1.8 years) were recruited from the McMaster Children's Hospital for this study. An a priori sample size calculation was conducted based on the FMD effect size and determined 51 participants per groups was required to have 80% statistical power. Despite this targeted sample size, difficulties in recruitment and a limited time for the preliminary assessment enabled 30 participants to be included in the study (CIC, n=21 and CON, n=9). All assessments were approved by the Hamilton Integrated Research Ethics Board.

The breakdown of participants per subgroup can be seen in Table 1. Inclusion criteria for the study were ages 7-17 years and a confirmed CIC for at least a year. Children were excluded if they had been hospitalized in the past three months and testing sessions were re-scheduled if the children presented with any symptoms of illness two weeks prior to their vascular assessment.

2.2 Study Design

A cross-sectional study design was implemented to assess potential differences in traditional and emerging CVD risk indicators between pediatric populations with chronic inflammatory disease and healthy, age- and sex-matched controls. All testing was conducted in the morning prior to engaging in any physical activity and following a 12 hour fast. Participants first underwent anthropometric measurements including height from a calibrated stadiometer, weight using a digital scale (Tanita BWB-800S, Alrington, IL) and BMI using a standardized equation. All testing sessions began with 10 minutes of supine rest followed by a 12-hour fasted blood sample by a trained researcher in a temperature-controlled room. The acquisition of the blood sample was then followed by another 10-minute period of supine rest before the vascular measurements were taken. All measurements were completed by a team of six trained researchers in the Vascular Dynamics Lab at McMaster University in Hamilton, Ontario. All data analysis was completed by a single trained researcher.

2.3 Laboratory Measurements

2.3.1 C-Reactive Protein

Fasted blood samples were collected into EDTA-treated vacutainers and were centrifuged within 30 minutes of collection. The plasma was stored in aliquots and frozen at -80°C until later analysis. A high sensitive enzyme linked immunsorbent assay (ELISA) (Abcam CRP Human SimpleStep ELISA Kit) was

used to quantify the amount of CRP in the plasma samples. The plasma samples were diluted 10,000-fold as described in the Abcam CRP Human SimpleStep ELISA Kit handbook and capture and detector antibodies were then added to the samples to bind to the CRP protein. The samples were then placed in anti-tag antibody coated wells in duplicate and incubated. The first two columns of wells contained serially diluted standards for calibration. The wells were washed to remove unbound material and TMB substrate was added and incubated in a dark room. Following incubation, a stop solution was added which finalized the colour change of the sample and was then analyzed for optical density at 450 nm using Multiskan Spectrum (Skanit, Research Edition 2.4.2, Thermo Electron Corpotration). The signal generated was proportional to the amount of bound substrate and compared to the standard curve to interpolate the CRP concentration in mg/L.

2.3.2 Dyslipidemia

Fasted blood samples were centrifuged following collection and the serum was frozen at -80°C until later analysis by the McMaster Core Laboratory. Total cholesterol was measured using a 7D62 Cholesterol Reagent Kit (Architect cSystems Assays, Abbott Laboratories, Abbott Park, IL), HDL cholesterol was measured using a 3K33-21 Ultra HDL Reagent Kit (Architect cSystems Assays, Abbott Laboratories, Abbott Park, IL), and triglycerides were measured using a

7D74 Triglyceride Reagent Kit (Architect cSystems Assays, Abbott Laboratories, Abbott Park, IL). From these values, LDL cholesterol was calculated using Equation 1. All lipids were reported as concentrations in mmol/L.

Equation 1. LDL= Total Cholesterol – (Triglyceride x 0.458 + HDL)

2.4 Carotid Artery Stiffness and cIMT

High resolution, two-dimensional, B-mode ultrasound images were used to capture images of the carotid artery along with simultaneous applanation tonometry to measure the compliance and distensibility of the carotid artery. With the participant in the supine position, a single-lead electrocardiograph (model ML 132; AD Instruments Inc., Colorado Springs, CO, USA). was continuously recorded for 10 consecutive heart cycles while longitudinal ultrasound images of the left common carotid artery were obtained. Two additional 10-beat recordings were obtained simultaneous to the acquisition of carotid artery blood pressure waveforms taken on the contralateral common carotid artery, using a hand-held tonometer (model SPT-301; Millar Instruments, Houston, TX). The images were then stored offline in Digital Image and Communications in Medicine (DICOM) form (Figure 2) for later analysis with a semi-automated tracking system (Artery Measurement System (AMS) II, Version 1.141; Gothenburg, Sweden) to measure the diameter of the internal lumen to quantify the amount of arterial expansion during each cardiac cycle. This software enables the investigator to choose a

region of interest (ROI) and detects the borders of the arterial wall according to varying degrees of contrast brightness. The investigator then scanned through each frame to ensure that the walls were properly tracked and manually manipulated the borders if required. The changes in diameter and pressure were used to calculate common carotid artery compliance and distensibility according to the equations listed below:

$$\textbf{Equation 2.}\ Compliance = \frac{\pi\left(\frac{dmax}{2}\right)^2 - \pi\left(\frac{dmin}{2}\right)^2}{PP}$$

$$\textbf{Equation 3.}\ Distensibility = \frac{\pi\left(\frac{dmax}{2}\right)^2 - \pi\left(\frac{dmin}{2}\right)^2}{\pi\left(\frac{dmin}{2}\right)^2 \ x\ PP}$$

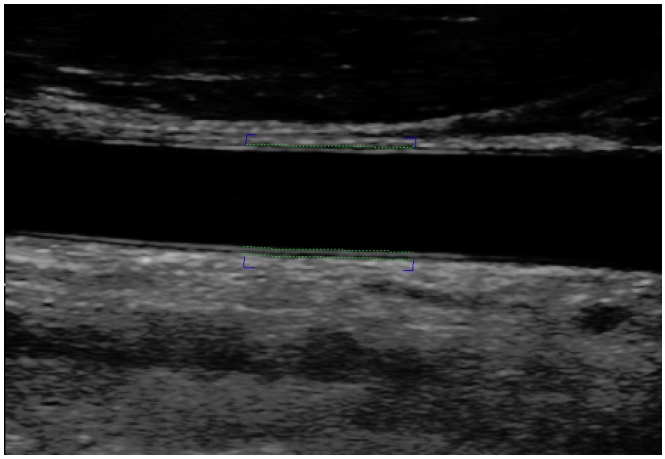


Figure 3. Example of a carotid DICOM image being analyzed through AMS for arterial lumen diameter in compliance and distensibility measures.

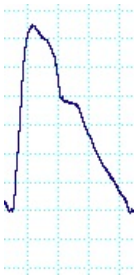


Figure 4. An example pulse pressure wave from the common carotid artery generated from the tonometer

Using the same semi-automated tracking system, cIMT was measured through visualization of the arterial borders on the far wall of the common carotid artery including both the intima to media to calculate the intima media thickness. The end-diastolic frames were extracted and analyzed at 100 sites per frame.

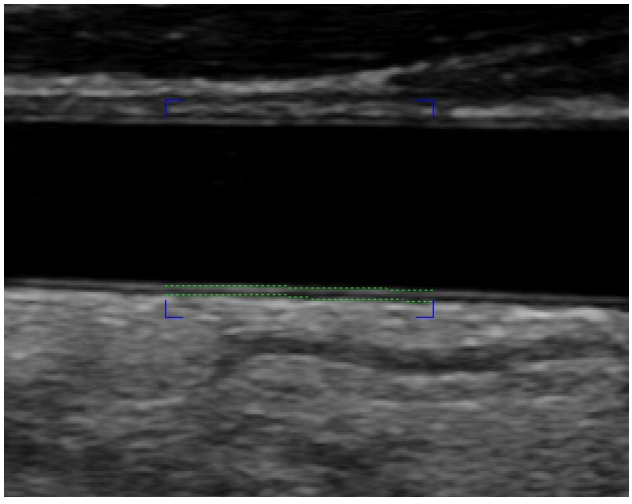


Figure 5. A DICOM image displaying the measurement of the intima-media thickness

2.5 Pulse Wave Velocity (PWV)

2.5.1. Applanation Tonometry

A hand held pressure transducer, known as a tonometer, was held on the cutaneous surface over the common carotid artery in the neck at the location of the strongest detectable pulse. The tonometer (Mikro-Tip Catheter Transducer, model SPT-301, Millar Instruments Inc., Houston, TX) was held firmly in place to allow the intra-arterial pressure to be to be transmitted to the micromanometer probe tip (Davies & Sruther, 2003). The tonometer was connected to an interface unit (Transducer Control Unit, model TCB-600, Millar Instruments Inc., Houston, TX) that served to calibrate the analogue signal before it was converted to a digital signal through the data acquisition system (PowerLab, model ML870, ADInstruments Inc., Colorado Springs, CO). The final result was a pressure wave measured in mmHg that was stored and analyzed on LabChart (Version 7, ADInstruments Inc., Colorado Springs, CO).

2.5.2. Infrared Photoplethysmograph (PPG)

An infrared PPG sensor (IR Plethysomograph, model MLT1020PPG, ADInstruments, Colorado Springs, CO) was placed on the cutaneous surface over the dorsalis pedis artery in the foot and held on through a Velcro strap at the

location of the strongest detectable pulse. PPG measures pulsatile blood flow through a built-in infrared light transmitter and photoelectric receiver which produces volume waveforms (Mackenzie et al., 2002). The PPG sensor was directly connected to the data acquisition system to be recorded simultaneously to the the carotid waveforms and ECG signal. The PPG signals were band-pass filtered to remove frequencies lower than 5MHz and higher than 30MHz to assist in the identification of the foot of each waveform.

2.5.3. Pulse Transit Time (PTT)

The PTT (Δt) is the time the pulse takes to travel from the carotid artery to the dorsalis pedis artery during simultaneous acquisition of the respective waveforms. PTT is calculated by a subtraction method (Equation 4) (Weber et al., 2009) which requires the time delay from ventricular depolarization (ECG-R spike) and the arrival of the pressure wave at the carotid (ECG-carotid) to be subtracted from the time delay between ventricular depolarization and the arrival of the pressure wave at the dorsalis pedis artery (ECG-DP):

Equation 4: PTT = (ECG-DP) – (ECG-carotid)

The arrival of the pressure wave was determined by the foot of the waveform which corresponds to the minimum point on the digitally filtered signal at end

diastole right before the sharp inflection during systole (Nichols & O'Rourke, 2005).

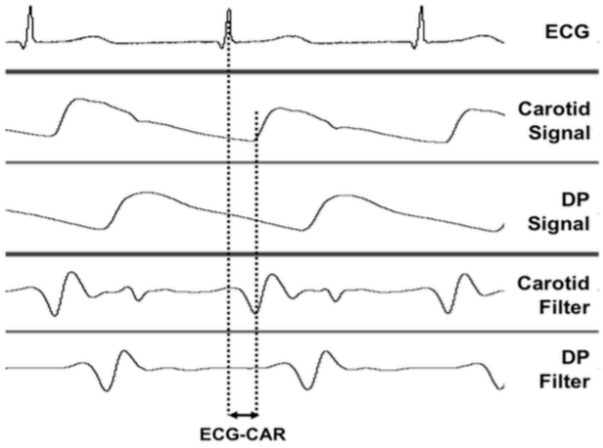


Figure 6. Calculation of the PTT (Δt) using digital band-pass filters.

2.5.4. Pulse Wave Travel Distance

The pulse wave travel distance was estimated by measurements along the body surface with an anthropometric tape measure across the body surface to the nearest 0.5 cm. Weber and colleagues (2009) emphasized the importance of a proper estimation of the pulse wave travel distance. After comparing several methods of estimation of pulse wave travel distance and comparing the findings to both invasive measurements of arterial stiffness through catheterization and measurement non-invasive PWV assessment, it was determined the best way to estimate carotid to femoral pulse wave travel distance was by carotid–femoral minus carotid–suprasternal notch distances (Weber et al., 2009). Based on this

theory, the distance between the suprasternal notch (an anatomical marker for location of ventricular depolarization) and the common carotid artery was measured (SN-carotid). This was followed by a measurement from the suprasternal notch to the dorsalis pedis artery in the foot (SN-DP). These distances were then inputted into Equation 5 to account for the pressure waves travelling to the carotid and dorsalis pedis arteries simultaneously and in opposite directions.

Equation 5 – Distance = (STN-carotid) – (STN-DP)

With both the PTT (Δt) and estimation of the arterial path distance calculated, these values can be entered into Equation 6 to get whole body PWV (O'Rourke et al., 2002).

Equation 6 $PWV = \frac{D}{\Delta t}$

2.6 Flow mediated dilation (FMD)

The Vascular Dynamics Lab standard operating procedures of the FMD test were used to assess endothelial function of the brachial artery. With the participant in the supine position, the left arm was positioned roughly 80° from the body and immobilized so that an optimal image of the brachial artery could be obtained. A sphygmomanometric cuff was placed on the forearm below the medial epicondyle and remained deflated while baseline ultrasound images of the

brachial artery were obtained. Longitudinal brightness mode (B-mode) ultrasound images of the left brachial artery were obtained using a 10MHz linear array probe (Vivid Q, GE Medical Systems, Horten, Norway) in combination with pulse wave Doppler acquisition of blood flow velocity. To create the flow stimulus, the forearm cuff was instantaneously inflated by a rapid cuff inflator (Hokanson E20, Hokanson Inc., Bellevue, WA). to a supra-systolic pressure of 50 mmHg above systolic pressure. Immediately following the five-minute duration, the pressure in the cuff was released and the reactive hyperemic blood velocity signals and ultrasound images were subsequently collected for three minutes.

All images were stored offline and processed by extracting the end diastolic frames of the ultrasound images and stacked through Sante DICOM Editor 3D (Santesoft LTD, Athens, Greece). Analysis was then completed on all end-diastolic frames using AMS for a specific ROI. The peak diameter was determined as the single largest diameter during reactive hyperemia. The absolute FMD (mm) and relative FMD (%FMD) were then calculated according to the following equations:

Equation 4. *Absolute FMD* = Peak Diameter (mm) – Baseline Diameter (mm)

Equation 7. *Relative FMD* = $\left(\frac{Absolute\ FMD}{Baseline\ Diameter}\right) x\ 100\%$

The magnitude of the shear stimulus was measured as the area under the

curve (AUC) of the shear rate stimulus. Mean blood flow velocity for the reactive hyperemia velocity profile was calculated using EchoPac PC software (Version 110.0.2; GE Medical Systems, Horten, Norway) and inputted into the following equation along with baseline arterial diameter:

$$\textbf{Equation 8.}\ Shear\ Rate = 8x\ \frac{Velocity}{Diameter}$$

The area under the curve of the shear rate was then calculated by plotting the mean blood velocities and calculating the area on the graph using GraphPad Prism (Version 6.03, GraphPad Software, Inc., California, USA).

The participants were asked to complete a brief questionnaire regarding physical activity levels in the past 24 hours, the time of their last meal and details of the consumption of certain substances such as vitamin C, nitrites and/or caffeine. There are a number of factors that can influence the flow-mediated vascular reactivity such as physical activity in the hours leading up to the test as well as the consumption of high-fat foods, caffeine, vitamin C and tobacco use (Corretti et al., 2002). Although participants were tested first thing in the morning in a fasted state, the questionnaire was given to help control for these factors.

2.7 Resting Blood Pressure

Resting blood pressure was assessed in both supine and seated positions after 10 minutes of rest using a GE CARESCAPE V100 DINAMAP. Arm

circumference was measured to ensure appropriate sized cuffs were used. For both positions, a minimum of four measurements of resting brachial artery blood pressure were obtained using an automated sphygmomanometer to obtain systolic, diastolic and mean blood pressure. The first measurement was discarded and the following three measurements were averaged if SBP was within 5 mmHg. If there was substantial variation in these three measurements (i.e. greater than 5 mmHg difference), then a fifth measure was recorded. Blood pressures were reported as raw scores and percentiles were determined based on age, sex and height (Ouspensky, 2004).

2.8 Body Mass Index (BMI)

BMI was used as an index of body mass composition since it has been shown to be a reliable surrogate for adiposity for children with a chronic disease (Warner et al., 1997). Standing height was measured using a calibrated stadiometer to the nearest 0.5cm without shoes. Body mass was measured using a digital scale (Tantita BWB-800S, Arlington Heights, IL) to the nearest 0.1kg while the participant was wearing light clothing and no shoes. Two measurements were taken for both variables and a third measurement was conducted if the standing height differed by more than 0.5 cm and weight by more than 0.4 kg. The average of both standing height and body mass were reported and subsequently entered into the following equation to calculate BMI:

Equation 9. $BMI = \frac{Mass\ (kg)}{Height\ (m)\text{^}2}$

The BMI scores were reported as raw scores and converted to percentile ranks according BMI-for-age growth charts from the Centers of Disease Control for children aged 2-20 years.

2.9 Statistical Analysis

Independent samples student's t-test was used to determine if there were differences between the chronic inflammatory group (CIC) and the healthy controls (CON) on all measurements that were normally distributed. A Kolmogorov-Smirnov test was used to test for normality and the Levene's test was used to test for homogeneity of variance. Data that were non-normally distributed were compared using a Mann-Whitney U test. Due to the high proportion of children with JIA in our sample, one-way ANOVAs were used to assess the differences between children with JIA, healthy controls (CON) and all other CIC conditions (CF, T1DM and IBD) grouped together (INFL) with a Bonferonni post-hoc analysis. A Kruskal-Wallis test was used to assess the differences between JIA, CON and INFL for data that were non-normally distributed. IBM SPSS Statistics 22 was used for all analyses and significance was set at $p<0.05$.

CHAPTER 3 – RESULTS

3.1 Group Differences (CIC vs. CON)

3.1.1. Participant Characteristics

There were no group differences in participant characteristics between the children with CIC and the healthy, sex-and-age matched controls (Table 1). Both groups were of similar age, height, weight and BMI. There were no differences in resting supine systolic, diastolic and mean arterial blood pressure as well as resting supine heart rate. Similar inflammatory levels were also found between both groups as indicated by concentrations of plasma CRP. Three children in the CIC group were excluded from the CRP analysis due to refusal of a blood draw (CIC, n=18) while two children were excluded from the control group due to insufficient quantities of plasma for analysis (CON, n=7). There were no differences in blood lipids between the two groups (Table 1).

3.1.2. Carotid Artery Measurements

Outcomes for baseline cIMT, distensibility and compliance are reported in Table 2. There were no group differences on any of these measures between the two groups. One participant from the CIC group was excluded from the distensibility and compliance analysis due to inadequate carotid pulse pressure waveforms (CIC, n=20).

Table 1. Participant characteristics of the study population divided by group (CIC vs. Control) with significance set to $p<0.05$. CIC= JIA (n=11), INFL (n=10), CON (n=9)

	CIC (n=21)	Control (n=9)	Significance
Age (years)	12.7 ± 2.3	13.1 ± 1.8	0.34
Sex (M/F)	13 (M), 8 (F)	6 (M), 4 (F)	-
Height (m)	1.6 ± 0.1	1.6 ± 0.1	0.51
Weight (kg)	50.0 ± 14.7	55.1 ±9.2	0.38
BMI (kg/m^2)	19.9 ± 3.6	21.2 ± 2.5	0.35
BMI percentile	50 ± 33	60 ± 27	0.67
RHR (bpm)	65 ± 10	62 ± 9	0.46
SBP (mmHg)	103 ± 9	108 ± 9	0.14
SBP percentile	55 ± 25	65 ± 19	0.71
DBP (mmHg)	60 ± 4	59 ±3	0.93
DBP percentile	64 ± 19	55 ± 13	0.82
MAP (mmHg)	76 ± 5	77 ± 7	0.63
Total cholesterol (mmol/L)	4.2 ± 0.70	4.1 ± 0.54	0.85
HDL (mmol/L)	1.2 ± 0.25	1.3 ± 0.39	0.68
LDL (mmol/L)	2.4 ± 0.56	2.4 ± 0.39	0.99
Triglyceride (mmol/L)	1.2 ± 0.86	1.0 ± 0.51	0.76
CRP (mg/L)	0.49 ± 0.4	0.41 ± 0.3	0.63

Values are represented as means ± SD. *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial blood pressure, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *CRP* C-reactive protein. * $p<0.05$ between groups.

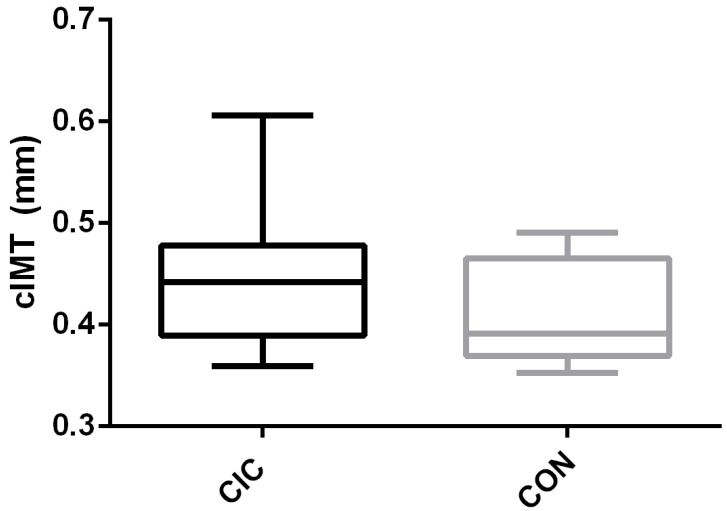


Figure 7. Comparison of cIMT (mm) between CIC (n=21) and CON (n=9).

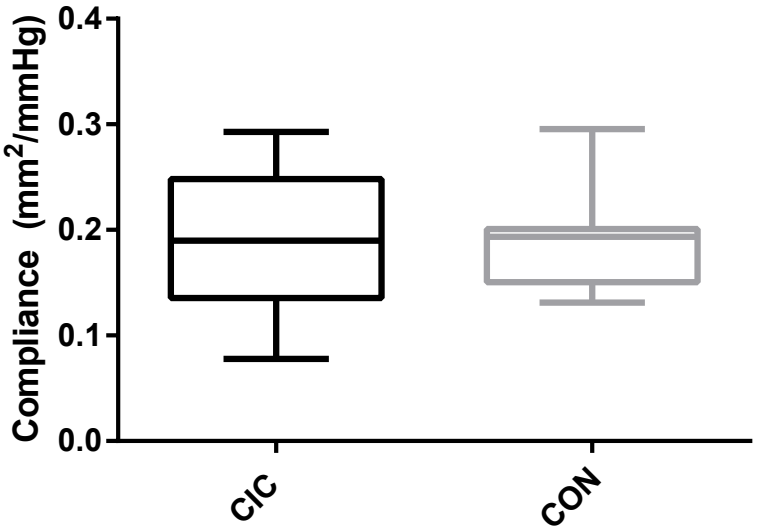


Figure 8. Comparison of carotid compliance (mm2/mmHg) between CIC (n=20) and CON (n=9)

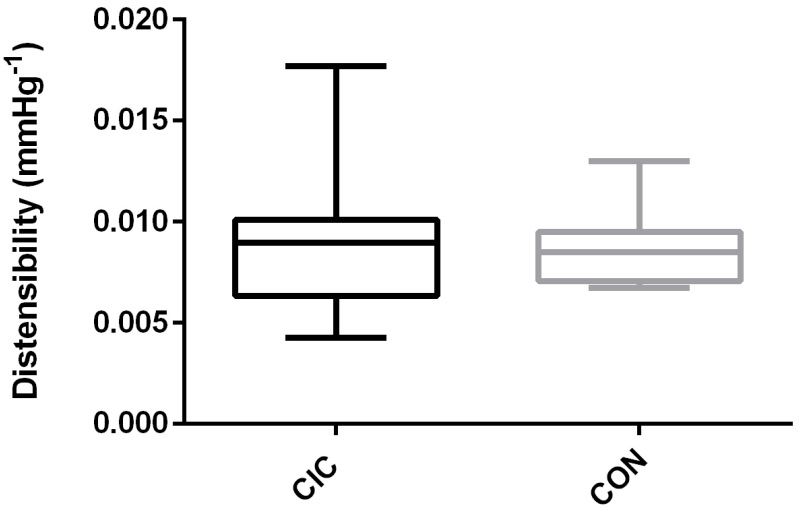


Figure 9. Comparison of carotid distensibility between CIC (n=20) and CON (n=9)

3.1.3. Pulse Wave Velocity (PWV)

There were no differences between the two groups on whole body PWV (Table 2 and Figure 10). One participant from CIC was removed for PWV analysis due to inadequate data quality of the pulse pressure waves from the carotid artery (CIC, n=20).

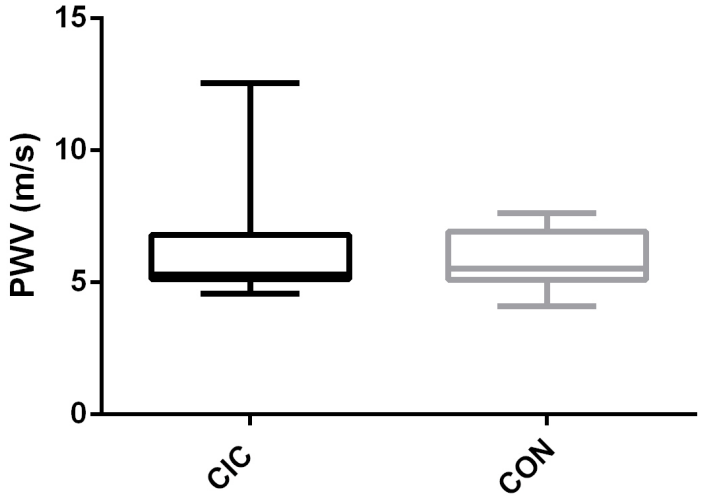


Figure 10. Comparison of whole body PWV (m/s) between CIC (n=20) and CON (n=9)

Table 2. Carotid artery measurements divided by group (CIC vs. Control). Significance set at $p<0.05$.

	CIC	CON	Significance
cIMT (mm)	0.44 ± 0.06	0.41 ± 0.05	0.18
Distensibility ($mmHg^{-1}$)	0.009 ± 0.003	0.008 ± 0.002	0.40
Compliance ($mm^2/mmHg$)	0.190 ± 0.063	0.190 ± 0.045	0.88
PWV (m/s)	6.11 ± 1.92	5.80 ± 1.13	0.74

Values are represented as means ± SD. *cIMT* carotid intima media thickness. * $p<0.05$ between groups

3.1.4. Flow Mediated Dilation (FMD)

All outcomes of the FMD test are reported in Table 3. Two participants from the CIC group were removed from analysis due to inadequate ultrasound

image quality during reactive hyperemia post-occlusion (CIC, n=19). The healthy controls had significantly greater pre-occlusion brachial baseline diameter (mm) and peak diameter (mm) during reactive hyperemia compared to children with CIC. Differences in baseline diameter were allometrically scaled (Atkinson et al., 2013) and revealed that the healthy controls reported a significantly greater %FMD compared to the children with a CIC (Fig 1, Table 3). After adjustment for shear rate during the reactive hyperemia response, normalized %FMD ($\%FMD/SR_{AUC}$) was greater in the controls when compared to the CIC group. There were no group differences seen in shear rate (SR) or time to peak (TTP) diameter during the ischemic reactive hyperemia response.

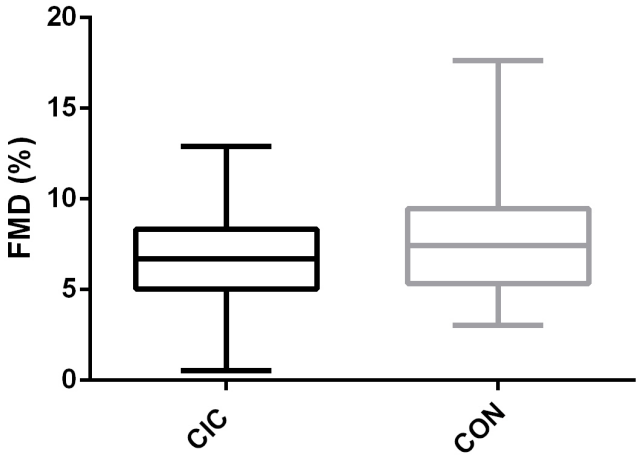


Figure 11. Comparison of scaled FMD (%) between CIC (n=19) and CON (n=9)

Table 3. Flow mediated dilation (FMD) outcomes between groups (CIC vs. Control). Significance set to $p<0.05$.

	CIC (n=19)	Control (n=9)	Significance
Pre-occlusion diameter (mm)	2.8 ± 0.4	3.4 ± 0.5*	<0.01
RH peak diameter (mm)	3.0 ± 0.4	3.8 ± 0.5*	<0.01
Absolute FMD (mm)	0.22 ± 0.16	0.32 ± 0.10	0.09
Scaled FMD (%)	6.6 ± .03	11.0 ± 0.03*	0.01
SR (s^{-1})	1191.4 ± 372.0	1170.3 ± 597.9	0.91
Normalized FMD ($\%FMD/SR_{AUC}$)	$5.5x10^{-3} \pm 1.9x10^{-3}$	$1.0x10^{-2} \pm 7.5x10^{-3}$*	0.02
Time to Peak (s)	27.9 ± 12.9	34.0 ± 11.2	0.10

Values are represented as means ± SD. * $p<0.05$

3.1.5. Univariate Analysis of Covariance (ANCOVA) – Age as a covariate

Age is known to be related to certain indices of vascular health (CITE), therefore a univariate analysis of covariance was conducted for %FMD using age as a covariate. After making this adjustment, the differences between groups for %FMD remained unchanged.

3.2 Comparison of children with JIA, other inflammatory conditions (INFL) and healthy controls (CON)

3.2.1. Participant characteristics

The participant characteristics for the JIA, INFL and CON groups can be seen in Table 4. There were no differences in age, RHR or any of the hemodynamic (SBP, DBP and MAP). Similar inflammatory levels were seen in

all three populations based on CRP values. Children with other inflammatory conditions (INFL) had a lower BMI when compared to healthy controls (CON) and children with JIA.

Table 4. Participant characteristics between groups (JIA vs. INFL vs. CON). Significance set at $p<0.05$

	JIA (n=11)	INFL (n=10)	CON (n=9)	Significance
Age (years)	12.6 ± 2.9	12.4 ± 1.7	13.4 ± 1.9	0.63
BMI (kg/m^2)	21.7 ± 3.9	17.8 ± 1.8*	21.2 ± 2.5	0.02
RHR (bpm)	66 ± 12	65 ± 8	62 ± 9	0.75
SBP (mmHg)	103 ± 8	103 ± 10	108 ± 10	0.29
DBP (mmHg)	60 ± 5	59 ± 4	59 ± 3	0.83
MAP (mmHg)	76 ± 5	76 ± 6	77 ± 8	0.92
CRP (mg/L)	0.66 ± 0.54	0.30 ± 0.30	0.41 ± 0.36	0.19
LDL (mmol/L)	2.6 ± 0.22	2.4 ± 0.15	2.2 ± 0.19	0.38
HDL (mmol/L)	1.3 ± 0.10	1.3 ± 0.14	1.1 ± 0.08	0.45
TC(mmol/L)	4.4 ± 0.30	4.1 ± 0.21	3.9 ± 0.21	0.50
TG(mmol/L)	1.0 ± 0.26	0.92 ± 0.17	1.4 ± 0.30	0.55

3.2.2. Carotid Artery Measurements

Outcomes for baseline cIMT, distensibility and compliance between JIA, INFL and CON are reported in Table 5. There were no group differences on either cIMT, distensibility or compliance (Figure 10). One participant from the JIA

group was excluded from the distensibility and compliance analysis due to inadequate carotid pulse pressure waveforms (JIA, n=10).

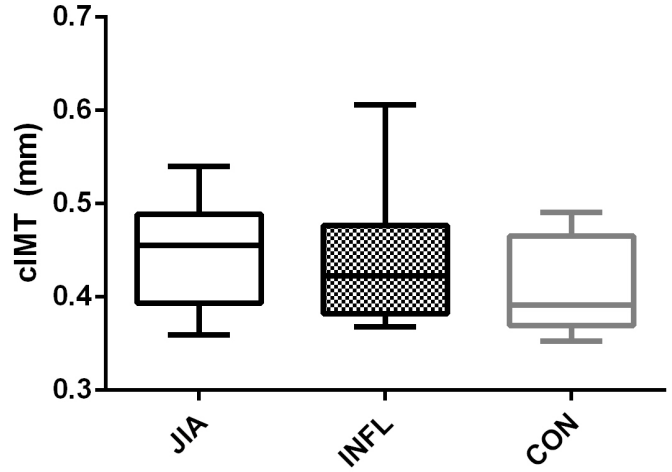


Figure 12. A comparison of carotid IMT (mm) between JIA (n=11), INFL (n=10) and CON (n=9)

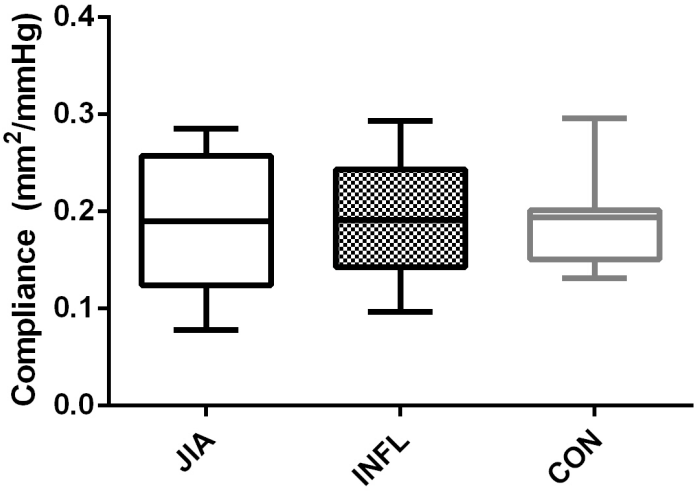


Figure 13. A comparison of carotid compliance (mm^2/mmHg) between JIA (n=10), INFL (n=10) and CON (n=9)

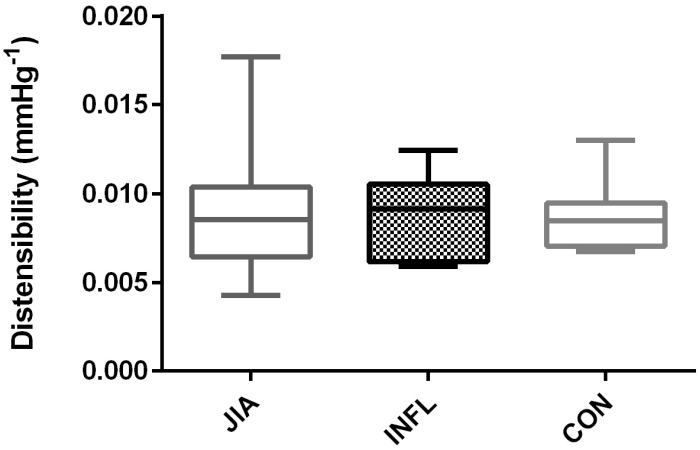


Figure 14. Comparison of carotid distensibility between JIA (n=10), INFL (n=10) and CON (n=9)

3.2.3 Pulse wave velocity (PWV)

There were no group differences in whole body PWV between JIA, INFL and CON (Table 5, Figure 11). One participant was removed from the JIA group (JIA, n=10) due to poor quality of the pulse pressure waveforms from the carotid artery.

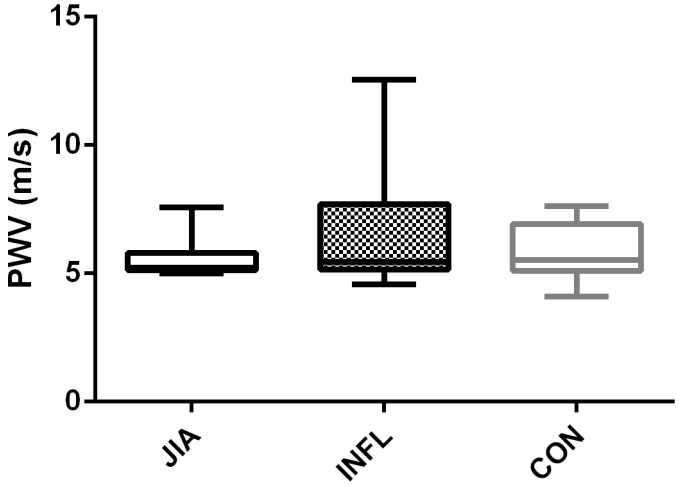


Figure 15. A comparison of whole body PWV between groups JIA (n=10), INFL (n=10) and CON (n=9).

Table 5. Arterial stiffness and cIMT between groups (JIA vs. INFL vs. CON). Significance was set at $p<0.05$

	JIA (n=10)	INFL (n=10)	CON (n=9)	Significance
Distensibility ($mmHg^{-1}$)	$9x10^{-3} \pm 4x10^{-3}$	$8x10^{-3} \pm 2x10^{-3}$	$8x10^{-3} \pm 2x10-^{3}$	0.93
Compliance ($mm^2/mmHg$)	0.17 ± 0.09	0.19 ± 0.06	0.19 ± 0.05	0.74
PWV (m/s)	5.6 ± 0.91	6.6 ± 2.5	5.8 ± 1.1	0.58
cIMT (mm)	0.45 ± 0.06	0.44 ± 0.07	0.41 ± 0.05	0.41

3.2.4. Flow-Mediated Dilation (FMD)

All outcomes of the FMD test are reported in Table 6 (Figure 12). One participant from the JIA group and one participant from the INFL group were

removed from analysis due to inadequate ultrasound image quality during reactive hyperemia post-occlusion (JIA, n=10; INFL, n=9). The CON group had higher pre-occlusion brachial baseline diameter (mm) and peak diameter (mm) during reactive hyperemia compared to the JIA and INFL groups ($p<0.01$ for both). There were no differences between the three groups for absolute FMD ($p=0.16$) and a trending significance towards a higher %FMD ($p=0.05$) for the CON group compared to both the JIA and INFL groups. Differences in baseline diameter were allometrically scaled and revealed that the healthy controls reported a greater %FMD compared to JIA and INFL ($p=0.04$). After adjustment for shear rate during the reactive hyperemia response, normalized %FMD (%FMD/SR_{AUC}) was similar between all three groups ($p=0.16$). There were no group differences seen in shear rate (SR) ($p=0.69$) or time to peak (TTP) diameter (p-0.49) during the ischemic reactive hyperemia response between any of the groups.

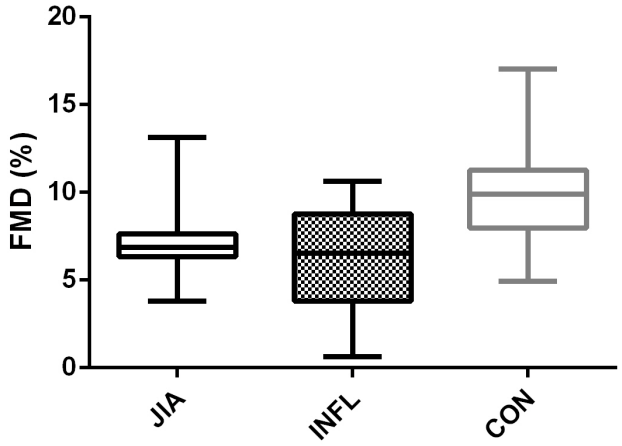


Figure 16. A comparison of scaled FMD (%) between JIA (n=10), INFL (n=9) and CON (n=9)

Table 6. Flow mediated dilation (FMD) outcomes between three groups (JIA vs. INFL vs. CON). Significance set to $p<0.05$.

	JIA (=10)	INFL (n=9)	CON (n=9)	Significance
Pre-occlusion diameter (mm)	2.8 ± 0.32	2.8 ± 0.53	3.4 ± 0.49*	<0.01
RH peak diameter (mm)	3.0 ± 0.32	3.0 ± 0.57	3.8 ± 0.51*	<0.01
Absolute FMD (mm)	0.26 ± 0.21	0.18 ± 0.10	0.32 ± 0.10	0.16
Relative FMD (%FMD)	6.3 ± 2.0	6.5 ± 3.1	9.6 ± 3.7	0.05
Scaled FMD (%FMD)	7.0 ± 3.1	11.0 ± 3.4	6.2 ± 3.1	0.04
SR (s^{-1})	1284 ± 292	1098 ± 434	1170 ± 597	0.69
Normalized FMD ($\%FMD/SR_{AUC}$)	$5x10^{-3}$ ± $1x10^{-3}$	$6x10^{-3}$ ± $2x10^{-3}$	$1x10^{-2}$ ± $8x10^{-3}$	0.16
Time to Peak (s)	27.8 ± 14.6	28.1 ± 11.6	34.0 ± 11.2	0.49

CHAPTER 4 – DISCUSSION

The aim of this study was to investigate the traditional and emerging CVD risk factors in children with a CIC and is the first of its kind to include children with a variety of inflammatory conditions in a comprehensive vascular health assessment protocol. The primary findings from this study suggest that arterial structure is similar between children with a CIC and their healthy peers; however, arterial function, as indicated by scaled FMD and $\%FMD/SR_{AUC,}$ was reduced in the CIC group. The groups did not differ in terms of age, anthropometric measurements, hemodynamic profiles (SBP, DBP, MAP, RHR) or inflammatory

levels. Due to the large proportion of participants in our sample with a diagnosis of JIA, further analyses were conducted to assess the differences in vascular parameters in children with JIA, healthy controls and the remainder of inflammatory conditions (CF, T1DM, IBD) grouped as the INFL group. The findings from the three group analyses revealed minimal differences from the initial analysis except for an attenuation in the differences seen in $\%FMD/SR_{AUC}$ and a reduced BMI in the INFL group when compared to JIA and CON groups.

The endothelium is the primary regulator of vascular homeostasis and is responsible for the balance of vasodilatory responses, and for stimulation and inhibition of smooth muscle proliferation and fibrinolysis (Davignon and Ganz, 2004). When the endothelium becomes damaged from factors such as dyslipidemia, oxidative stress or inflammation, these processes are interrupted. The ensuing endothelial dysfunction is an early event in the atherosclerotic process (Widmer & Lerman, 2014). In the current study, children with a CIC demonstrated lower brachial artery endothelial function (reduced %FMD and $\%FMD/SR_{AUC}$) compared to healthy controls ($p<0.01$ and $p=0.02$, respectively). These findings supported those of previous studies that have examined endothelial function in children with IBD and T1DM (Aloi et al., 2012; Järvisalo et al., 2004). A cross-sectional study assessing FMD in 45 children with T1DM reported impaired total dilation response and peak diameter during reactive hyperemia when compared to healthy controls (Järvisalo et al., 2004). Similarly, decreased

endothelial function has been reported in pediatric populations with IBD with a larger magnitude of impairment noted in children with a greater disease severity (Aloi et al., 2012). Vlahos and colleagues (2011) reported a 30% reduction in endothelial function in children with JIA compared to healthy controls, although these differences were attenuated when adjusting for erythrocyte sedimentation rate (ESR), ICAM-1 and glucose levels. The results from our three group analysis revealed a reduced %FMD in children with JIA (mean %FMD of 7%) when compared to healthy controls, making this the first study to report endothelial dysfunction in this population. Although there are no true definitive cutoff values for endothelial dysfunction in children, Jarvisalo and colleagues (2004) derived normative FMD data from 105 healthy children and determined endothelial dysfunction to be present when the peak %FMD is below 3.3%. According to this cutoff value, one participant from the JIA group and one participant from the INFL group in the current study would be considered to have endothelial dysfunction.

Shear stress refers to the force per unit area as the blood flows through the artery and exerts a tangential force on the endothelium. The deformation of the endothelium from the shear stress stimulates the release of NO, a potent endothelium-derived vasodilator, through mechanotransduction (Davies, 2009). In order to quantify the shear stress response, we calculated the shear rate during the reactive hyperemia phase of the FMD test. There were no differences in shear rate

between children in the CIC group and the healthy controls suggesting similar ischemic-induced reactive hyperemia responses between the two groups, despite the differences in %FMD and %FMD/SR_{AUC}. The current study findings related to shear rate agree with those of an earlier study investigating the relationship between four indices of SR_{AUC} and FMD response where no correlations were found between the two measures for children (Thijssen et al., 2008). Shear rate therefore, does not seem to be a significant predictor of FMD response but is, instead, dependent on factors such as wall elasticity, thickness and resting baseline diameter.

Time to peak (TTP) diameter during reactive hyperemia has shown variability both between and within subjects (Liuni et al., 2010) but is believed to be shorter in younger individuals (Black et al., 2008). A study investigating the time course of FMD in younger (26.2 ± 3.3 years), older sedentary (57.3 ± 3.9 years) and older fit individuals (58.9 ± 5.1 years) found a shorter time to peak FMD in younger compared to both older sedentary and older fit individuals (Black et al., 2008). The authors speculate that this may be due to the arterial stiffening that occurs with ageing or the possibility of reduced enzyme rate constants with age that could delay the production of hormone production and release from the endothelium (Black et al., 2008). Although not fully understood how it develops, longer time to peak (TTP) results have been shown to be associated with reduced vascular function (Padilla et al., 2009) although TTP

seems to vary considerably in children (Järvisalo et al., 2002). Our results demonstrate that there were no differences in TTP between the CIC group and controls thereby suggesting that these children have similar temporal reactivity in artery vasodilatory responses to the shear stress stimulus.

There were no significant differences in cIMT between the CIC group (0.44 ± 0.06mm) and the healthy controls group (0.41 ± 0.05mm). Despite the lack of published cutoff values for pediatric populations, the mean cIMT values for healthy adolescents has been reported to range from 0.38 to 0.40mm, with 0.47mm being reported as the 90th percentile (Jourdan et al., 2005). Based off of these values, the mean cIMT for the CIC group (0.44 mm) is well below the 90th percentile and the mean cIMT of healthy controls (0.41 mm) is close to the healthy range. The similarities in cIMT between groups is supported by some previous research which has demonstrated no differences in cIMT between healthy children and children with IBD (Aloi et al., 2015), JIA (Vlahos et al., 2011; Satija et al., 2014) and T1DM (Jarvisalo et al., 2004; Gunczler et al., 2002).

It should be noted, however, that there is some conflicting evidence in the literature for cIMT in pediatric populations with CICs. Dalla Pozza and colleagues (2007) published a study including 150 children with T1DM (13.8 ± 2.9 years) and 58 healthy controls (14.1 ± 3.1 years) in which they reported an increased cIMT in the children with T1DM. In fact, the mean cIMT of children with T1DM was found to be 0.46mm, with the highest cIMT in this population

measured at 0.55mm – a value above the suggested 90th percentile. Higher cIMT values have also been noted in children (mean age 13.3 ±3.9 years) who have been newly diagnosed with JIA (Ilisson et al., 2015), suggesting the presence of vascular pathologies despite a short disease duration. It has been speculated that the differences seen in IMT could be due to the differing measurement and analysis techniques utilized in different studies. Therefore, using a more systematic approach involving the implementation of ultrasound probes of similar resolution and standardized analysis techniques, whether it be manual tracing of the IMT or semi-automated tracking could improve agreement between studies.

Carotid distensibility and compliance were shown to be similar in all analyses including comparisons between the CIC group and controls and between the JIA, INFL and CON groups. Throughout the lifespan, carotid compliance and distensibility decreases due to the widely noted age-related increase in arterial stiffness (Mitchell et al., 2004). To date, there has only been one other published study that has examined carotid compliance and distensibility in this population (Satija et al., 2014). This previous study was conducted with a sample of 31 children with JIA and 31 healthy, matched controls with a mean age of 10.2 ± 4.0 years (Satija et al., 2014). The results from this study demonstrated differences in cross-sectional compliance between the two groups with the compliance measures being 20% lower for children with JIA compared to controls. The values for distensibility were also lower in T1DM by 18% although these differences did not

reach statistical significance (Satija et al., 2014).

Our results reveal that there were no differences in whole body PWV between the CIC group and controls, indicating preserved systemic arterial elasticity at this time point. To our knowledge, there have been no studies to date that have examined whole body PWV in these populations, but have rather focused on central PWV which is measured from the carotid to femoral artery. The lack of literature reporting whole body PWV makes it difficult for direct comparisons to previous literature; however, this method was chosen to provide maximal comfort for the children in avoiding accessing the femoral artery. As an alternative, whole body PWV was assessed from the right common carotid artery in the neck to the right dorsalis pedis artery in the foot. This adapted method has been piloted in a previous study from our lab and has demonstrated reliable measures in healthy children aged 2-6 years reporting a coefficient of variation of 3.5% (Currie et al., 2010).

Although the protocol was slightly different and assessing a smaller segment of the arterial tree, Heilman and colleagues (2009) found similar central arterial stiffness through assessment of aortic PWV between 30 children with T1DM (13.1 ± 3.6 years) and 30 healthy controls (13.2 ± 3.9 years). Additionally, Lurz and colleagues (2017) assessed central arterial stiffness through carotid to femoral PWV in 25 children with mild IBD and found comparable PWV to

published reference values. The findings from our study as well as the work from Lurz and colleagues (2007) supports the theory of a preserved arterial stiffness in children in with low disease activity or for those who may be in remission. Furthermore, given the age of the participants, it can be speculated that there has yet to be an adequate exposure of CVD risk factors as stiffening of the arterial walls is a phenomenon that typically manifests in later stages of CVD pathophysiology as demonstrated by the strong relationship between PWV and age (Relf et al., 1986; Vaitkevicius et al., 1993; Mitchell et al., 2004)

C-reactive protein (CRP) is an acute phase protein and marker of inflammation that has been shown to predict incident peripheral artery disease, myocardial infarction, stroke and sudden cardiac death (Ridker, 2003). In fact, normative CRP data from adults has been published which enables individuals to be categorized according to their risk for future CV events (Musunuru et al., 2008). Individuals with CRP levels below 1 mg/L are said to have a low risk, between 2-3 mg/L are at an intermediate risk and above 3 mg/L are at a high risk for CV events. In the current study, children with CIC demonstrated similar CRP levels compared to the healthy controls. In fact, nearly all participants were in the low risk category (CIC, n=20 of 21, CON, n=9 of 9) and only one participant was in the intermediate risk category with a CRP level of 1.97 mg/L. Based on the exclusion criteria of the study, we were excluding any participants who had been hospitalized in the last three months and children were required to be symptom

free of any common colds or symptoms of illness during the two weeks prior to their blood draw and vascular assessment. These results may provide evidence to suggest that if the inflammatory state is well controlled, similar values for both emerging and cardiovascular CVD risk factors may be obtained despite the predisposed elevated CVD risk that the children with inflammatory conditions are suggested to have. If true, this finding would provide sound reasoning to continue to develop and explore different avenues for effective therapeutic interventions for inflammatory conditions.

The similarities in inflammatory levels between the two groups limits the use of current inflammatory state to explain the endothelial dysfunction observed in the CIC group. We found a moderate, positive correlation between %FMD and SBP ($r=0.38$, $p=0.05$) indicating a possible relationship between SBP and the FMD response. However, %FMD was not correlated with BMI or levels of inflammation. It is possible that there may be a factor contributing to these differences in %FMD that has not been examined in this study. In fact, exercise training has been shown to elicit improved artery health believed to be related to the function of the endothelium (Dawson et al., 2013) as the reduction in future CVD risk is not well explained by the change in traditional CVD risk factors alone (Green et al., 2004). Exercise has the ability to produce different patterns of shear stress (Thijssen et al., 2009), specifically enhanced anterograde shear, which has shown to have beneficial effects on vascular function and upregulation in the

NO pathway (Thijssen et al., 2009). In fact, a previous study investigating the relationship between physical activity and FMD response in 45 healthy children (5-10 years) reported higher levels of habitual physical activity as a strong predictor of FMD (Abbott, Harkness, & Davies, 2002). Building on this finding, Hopkins and colleagues (2009) found a positive correlation between habitual physical activity, cardiorespiratory fitness and FMD/SR_{AUC} in healthy children aged 10-11 years of age. The children with the lowest fitness demonstrated the lowest FMD responses and the authors concluded that habitual physical activity and fitness were the best predictors of endothelial function (Hopkins et al., 2009). The implications of these findings is critical when assessing FMD in children with chronic inflammatory conditions as it is widely noted that children with JIA, T1DM, IBD and CF are less active than their healthy peers and that this relationship is worse for girls than for boys (Bohr et al., 2015; Nixon et al., 2001; Valerio et al., 2007; Werkstetter et al., 2012). Although habitual physical activity or fitness measures were not included in this analysis, this an area that could be further explored to help elucidate the increased endothelial dysfunction noted in these populations.

The results for BMI showed no differences between the CIC and CON groups, however, when the participants were broken into three groups, the INFL group demonstrated a reduced BMI (17.8 ± 1.8 kg/m^2) compared to children with JIA and controls. The results from the BMI analysis are not all that surprising as

over half of the children in the INFL group have a diagnosis of CF (n=6 of 10). Despite there being a lack of literature directly comparing BMI in CF and healthy matched controls, children with CF are consistently below the growth standards for height and weight (Parsons et al., 1993; Henderson et al., 1999) which are the two components required to measure BMI, implicating a tendency for a lower BMI in this population.

The blood lipid analysis revealed that there were no differences in total cholesterol, LDL, HDL or triglycerides between children with inflammatory conditions and healthy controls. The available literature pertaining to blood lipid profiles in children with inflammatory conditions provide varied results (Bakkaloglu et al., 1996; Ilowite et al., 1989; Tselepis et al 1999; Marangoni et al., 2011; Skolnik et al., 2016; Silverstein et al., 2005; Donaghue et al., 2007; Kim et al, 2014). The inconsistency regarding these results could potentially be explained by different laboratory techniques and assays used between research groups. Furthermore, the advancement of new technologies over the past decade may be able to improve the ability for differences to be detected. A larger sample size with consistent application of similar protocol may be able to help explain the lipid profiles in these patients. That being said, it is worth nothing that there was one participant with a CF diagnosis that had a total cholesterol level (5.36 mg/L) above the suggested cutoff levels for healthy children (Canadian Health Measures Survey, 2010). In addition, the recommended levels for HDL are >1.3 mmol/L.

The CIC group had a mean HDL level of 1.2 mmol/L whereas the healthy controls had a mean HDL level of 1.3 mmol/L. Despite this small difference not being statistically significant, it does put the CIC group in an at risk category which supports the importunate of looking into minimal clinically important differences in future studies.

The similarities in SBP and DBP seen in the participants in our study are consistent with previous literature in children with JIA, CF, T1DM and IBD (Ilisson et al., 2015; Satija et al., 2014; Sozeri et al., 2016; Vlahos et al., 2011; Skolnik et al., 2016; Emre et al., 2006; Järvisalo et al., 2004; Pozza et al., 2007; Stakos et al., 2005; Kim, Jang & Lee, 2014; Lurz et al., 2017). The findings pertaining to BP in the above mentioned populations are nearly unanimous in demonstrating similar hemodynamic profiles. Aloi and colleagues (2012) were the only authors to report higher DBP in 52 children with IBD. In our sample, all children were free of hypertension due to all of their SBP and DBP being below the 95th percentile.

4.2 Limitations

The present study is faced with several limitations which should be taken into consideration. Firstly, CRP is an acute phase protein meaning that its plasma concentration increases acutely in response to tissue injury or inflammation (Kushner, Rzewnicki, & Samols, 2006). It is possible that the cross-sectional design did not appropriately capture the baseline inflammatory state of these

individuals. The measurement of other inflammatory markers such as IL-6 or TNF-∝ could have given a more comprehensive view of inflammatory levels in the participants in this study.

In line with the common theme in previous literature, a larger sample size would help elucidate the relationship between vascular structure and function and various chronic inflammatory diseases. The original proposal of this study was anticipating a much larger sample size (n=180), which could have allowed for stratification of participants by disease group and increased the statistical power for some of these planned comparisons. With a larger sample group, the study would also be powered to run a regression to help assess potential relationships between the emerging and traditional cardiovascular risk factors for these populations. Recruitment rates were challenged by children becoming ill and scheduling around their busy lives with school, extracurricular activities and clinic visits. Due to the difficulty with recruitment, all chronic inflammatory conditions were grouped together for analysis with a much reduced sample size (n=30).

While all of the vascular measures in the current study are non-invasive and theoretically straightforward, the technical acquisition of data and interpretation may present some limitations. Data analysis is heavily dependent on high quality ultrasound images and pressure waves which require both a trained investigator and quality analysis software. Standardized operating procedures were used to minimize differences in results related to techniques and criteria for

data removal. There was one participant in which the data was excluded for FMD assessments due to significant movement during the reactive hyperemia image and another participant in which the data was excluded for PWV, distensibility and compliance due to inadequate data quality in pressure waves.

Lastly, the nature of a cross-sectional study reduces the ability to monitor any changes in measurements at multiple time points. In a physiological setting such as this, it is possible to have extraneous factors influencing the reactivity of the artery such as sympathetic stimuli, medications, room temperature, among others. For many of the participants, it was likely the first time they had experienced a FMD test in an unfamiliar environment which could have elicited a sympathetic response.

4.3 Future Directions

Future studies should aim to include a larger sample size to increase statistical power as well as stratify the participants based on their diagnosed inflammatory condition. This approach would enable researchers to look at differences both between, and within, groups. The current findings may help identify if there are any similar patterns between different inflammatory conditions. Additionally, it would be beneficial to include multiple inflammatory markers with measurements at multiple time points to get an accurate depiction of the inflammatory levels of all participants and avoid the bias from physiological fluctuations. A familiarization of the FMD test may be useful in a pediatric

population to help avoid a sympathetic response which could influence the reactivity of the brachial artery. If time had allowed, an assessment of day to day reliability of the emerging CVD risk factors would inform both the validity and reliability of the assessments obtained a single time point in these populations. Lastly, it would be beneficial to include physical activity and fitness data to explore the relationship between vascular structure and function and habitual physical activity. Elucidating this relationship may provide a framework for implementing an exercise intervention study for children with inflammatory conditions. If found to be successful, exercise could be used as an adjunct to current therapeutic interventions for these children which would have minimal side effects.

The findings form this study are preliminary findings contributing to the cardiovascular health in children with a chronic inflammatory condition: role of physical activity, fitness and inflammation (CHAMPION) study. The full analysis of this study will be completed on 300 children and will include the variables discussed in this thesis as well as TNF-α, IL-6, blood glucose, insulin, circulating endothelial progenitor cells, physical activity levels, cardiorespiratory fitness, muscle strength, motor control and mental health questionnaires. The final analyses of the CHAMPION study will provide information regarding the link between physical activity, fitness and inflammatory levels to the traditional and emerging CVD risk factors.

4.4 Conclusion

Although there were no differences noted in arterial structure, children with a CIC demonstrated decreased endothelial function compared to their healthy counterparts. This finding is essential in that it helps to identify an area for targeted intervention and/or prevention of future CV events as endothelial dysfunction is known to be an early event in the pathophysiology of atherosclerosis. Additionally, demonstrating similar arterial stiffness and cIMT between children with a CIC and healthy controls, provides evidence that the structural integrity of the artery is similar between these groups and any pathological disease related changes are not detectable using the current methods. These findings could be partially contributed to the low levels of inflammation seen in our sample and highlight the importance of controlling the inflammatory response early in life in these conditions. The introduction and encouragement of healthy lifestyle behaviors and appropriate medical interventions at this young age may be able to mitigate deleterious changes to the arterial wall. It should be noted that this study is faced with several limitations, such as sample size and cross-sectional design that warrant further, longitudinal investigation including physical activity data and a variety of inflammatory markers.

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Appendix A – Blood Pressure Tables for Children

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Figure 17. BP reference values for boys aged 1-10 years based on age and height percentiles. The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD and the 99th percentile is 2.326 SD above the mean (Ouspensky, 2004).

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Figure 18. BP reference values for boys aged 11-17 years based on age and height percentiles. The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD and the 99th percentile is 2.326 SD above the mean (Ouspensky, 2004).

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Figure 19. BP reference values for girls aged 1-10 years based on age and height percentiles. The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD and the 99th percentile is 2.326 SD above the mean (Ouspensky, 2004).

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Figure 20. BP reference values for girls aged 11-17 years based on age and height percentiles. The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD and the 99th percentile is 2.326 SD above the mean (Ouspensky, 2004).

Appendix B – Raw Data

Table 7 – Anthropometric data for the CIC group

Participant ID	Sex	Age (years)	Height (m)	Weight (kg)	BMI (kg/m^2)
CHAMP-2F-02	F	11.04	1.48	33.8	15.3
CHAMP-2F-03	F	15.01	1.58	52.6	20.0
CHAMP-2M-01	M	10.11			
CHAMP-2M-05	M	10.07	1.58	38.8	15.6
CHAMP-2M-09	M	14.04	1.39	38.8	20.0
CHAMP-2F-08	F	13.01	1.52	36.4	15.8
CHAMP-3F-02	F	17.20	1.60	63.9	24.5
CHAMP-3F-04	F	15.01	1.64	51.2	19.0
CHAMP-3F-05	F	17.01	1.66	66.7	24.4
CHAMP-3F-13	F	10.01	1.69	65.4	23.0
CHAMP-3M-01	M	9.11	1.44	38.6	18.6
CHAMP-3M-03	M	12.11	1.49	54.5	24.4
CHAMP-3M-07	M	14.03	1.66	42.1	15.3
CHAMP-3M-08	M	11.06	1.50	51.4	22.7
CHAMP-3M-11	M	9.01	1.29	29.8	17.6
CHAMP-3M-14	M	12.07	1.60	70.5	27.5
CHAMP-3M-15	M	12.11			

CHAMP-4F-01	F	14.04	1.62	48.1	18.4
CHAMP-4M-02	M	12.01	1.46	39.1	18.4
CHAMP-5M-01	M	12.05	1.54	44.3	18.8
CHAMP-5M-03	M	13.02	1.54	42.9	18.2

Table 8. Anthropometric data for the CON group

Participant ID	Sex	Age	Height	Weight	BMI
CHAMP-6F-02	F	14.05	1.64	59.8	22.2
CHAMP-6F-04	F	9.05	1.45	44.4	21.3
CHAMP-6F-07	F	13.06	1.65	54.2	19.9
CHAMP-6M-01	M	14.1	1.86	91.9	26.7
CHAMP-6M-03	M	14.02	1.72	61.35	20.7
CHAMP-6M-05	M	12.01			
CHAMP-6M-06	M	15.05	1.71	53.8	18.3
CHAMP-6M-08	M	15.03	1.69	57.5	20.2
CHAMP-6M-09	M	14.06	1.77	63.4	20.3

Table 9. Hemodynamic profiles for the CIC group

Participant ID	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	RHR (bpm)
CHAMP-2F-02	108	64	79	77
CHAMP-2F-03	113	67	84	65
CHAMP-2M-01	94	61	74	69
CHAMP-2M-05	99	55	71	53
CHAMP-2M-09	119	56	81	68
CHAMP-2F-08	108	61	79	68
CHAMP-3F-02	97	53	69	46
CHAMP-3F-04	100	55	71	66
CHAMP-3F-05	103	57	75	54
CHAMP-3F-13	100	58	74	69
CHAMP-3M-01	107	57	77	60
CHAMP-3M-03	108	65	84	67
CHAMP-3M-07	100	65	78	57
CHAMP-3M-08	97	67	79	58
CHAMP-3M-11	88	61	70	74
CHAMP-3M-14	107	64	72	78
CHAMP-3M-15	121	60	82	84
CHAMP-4F-01	91	55	70	69

CHAMP-4M-02	89	53	66	54
CHAMP-5M-01	107	59	78	57
CHAMP-5M-03	97	61	73	66

Table 10. Hemodynamic profiles for the CON group

Participant ID	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	RHR (bpm)
CHAMP-6F-02	100	57	72	64
CHAMP-6F-04	98	59	73	64
CHAMP-6F-07	112	61	79	73
CHAMP-6M-01	109	58	77	58
CHAMP-6M-03	108	58	77	53
CHAMP-6M-05	97	54	69	60
CHAMP-6M-06	111	59	78	46
CHAMP-6M-08	113	61	69	71
CHAMP-6M-09	128	66	95	71

Table 11. cIMT, distensibility (dist), compliance (comp) and PWV for the CON group

Participant ID	cIMT (mm)	Comp (mm^2/mmHg)	Dist($mmHg^{-1}$)	PWV(m/s)
CHAMP-2F-02	0.37	0.15	9.0 x10-3	9.5
CHAMP-2F-03	0.61	0.13	6.2 x 10-3	7.1
CHAMP-2M-01	0.52	0.29	1.1 x 10-2	5.2
CHAMP-2M-05	0.44	0.25	1.2 x 10-2	5.5
CHAMP-2M-09	0.46	0.15	5.9 x 10-3	12.5
CHAMP-2F-08	0.41	0.09	6.1 x 10-3	5.2
CHAMP-3F-02	0.39	0.20	9.0 x 10-3	5.1
CHAMP-3F-04	0.47	0.25	9.3 x 10-3	5.1
CHAMP-3F-05	0.41	0.19	7.1 x 10-3	5.4
CHAMP-3F-13	0.47	0.17	6.7 x 10-3	5.3
CHAMP-3M-01	0.38	0.13	5.7 x 10-3	5.0
CHAMP-3M-03	0.49	0.11	8.2 x 10-3	5.1
CHAMP-3M-07	0.36	0.19	8.9 x 10-3	7.6
CHAMP-3M-08	0.45			
CHAMP-3M-11	0.54	0.29	1.4 x 10-2	5.2
CHAMP-3M-14	0.44	0.27	1.8 x 10-2	7.0
CHAMP-3M-15	0.52	0.08	4.3 x 10-3	5.2
CHAMP-4F-01	0.39	0.24	1.0 x 10-2	5.1

CHAMP-4M-02	0.40	0.23	9.3 x 10-3	4.6
CHAMP-5M-01	0.37	0.16	7.2 x 10-3	6.1
CHAMP-5M-03	0.44	0.22	9.3 x 10-3	5.3

Table 12. cIMT, distensibility (dist), compliance (comp) and PWV for the CON group

Participant ID	cIMT(mm)	Comp(mm^2/mmHg)	Dist($mmHg^{-1}$)	PWV (m/s)
CHAMP-6F-02	0.47	0.16	7.0 x 10-3	5.5
CHAMP-6F-04	0.46	0.20	1.3 x 10-2	5.1
CHAMP-6F-07	0.35	0.14	7.2 x 10-3	5.5
CHAMP-6M-01	0.49	0.30	8.5 x 10-3	5.0
CHAMP-6M-03	0.39	0.19	7.1 x 10-3	7.2
CHAMP-6M-05	0.39	0.20	1.0 x 10-2	4.1
CHAMP-6M-06	0.40	0.13	6.7 x 10-3	6.6
CHAMP-6M-08	0.39	0.19	8.6 x 10-3	5.6
CHAMP-6M-09	0.35	0.19	8.5 x 10-3	7.6

Table 13. Brachial vascular dimensions and FMD response for the CIC group

Participant ID	Baseline diameter (mm)	Peak Diameter (mm)	FMD (mm)	FMD (%)
CHAMP-2F-02	2.3	2.4	0.16	6.8
CHAMP-2F-03	2.9	3.2	0.28	9.5
CHAMP-2M-01				
CHAMP-2M-05	3.34	3.4	0.11	3.2
CHAMP-2M-09	3.6	3.9	0.35	9.7
CHAMP-2F-08	2.7	2.8	0.10	3.7
CHAMP-3F-02	2.8	3.0	0.14	4.9
CHAMP-3F-04	2.6	2.8	0.17	6.6
CHAMP-3F-05	3.2	3.4	0.19	6.0
CHAMP-3F-13	3.1	3.3	0.15	4.9
CHAMP-3M-01	2.2	2.4	0.18	8.1
CHAMP-3M-03	2.7	3.1	0.28	8.6
CHAMP-3M-07				
CHAMP-3M-08	2.5	3.3	0.81	2.6
CHAMP-3M-11	2.6	2.6	0.16	6.3
CHAMP-3M-14	2.8	2.8	0.39	9.3
CHAMP-3M-15	1.9	3.0	0.19	6.1

CHAMP-4F-01	3.1	2.0	0.04	2.1
CHAMP-4M-02	3.0	3.3	0.17	5.4
CHAMP-5M-01	2.4	3.2	0.21	7.1
CHAMP-5M-03	3.3	2.7	0.26	10.7

Table 14. Brachial vascular dimensions and FMD response for the CON group

Participant ID	Baseline diameter (mm)	Peak Diameter (mm)	FMD (mm)	%FMD
CHAMP-6F-02	3.3	3.5	0.14	4.3
CHAMP-6F-04	2.9	3.3	0.25	8.3
CHAMP-6F-07	2.6	3.1	0.46	12.7
CHAMP-6M-01	3.7	3.9	0.25	6.7
CHAMP-6M-03	3.8	4.1	0.33	8.7
CHAMP-6M-05	3.0	3.4	0.34	11.5
CHAMP-6M-06	4.0	4.4	0.36	9.1
CHAMP-6M-08	4.0	4.5	0.47	11.9
CHAMP-6M-09	3.6	3.9	0.31	8.4

Table 13. FMD responses for the CIC group

Participant ID	Scaled FMD (%)	Normalized FMD (%FMD/SR_{AUC})	SR (s^{-1})	TTP (s)
CHAMP-2F-02	8.8	0.00586	1167.5	33.3
CHAMP-2F-03	8.3	0.00708	1341.6	35.5
CHAMP-2M-01				
CHAMP-2M-05	0.5	0.00499	641.6	30.9
CHAMP-2M-09	6.7	0.00859	1129.5	34.9
CHAMP-2F-08	4.1	0.00287	1289.6	21.9
CHAMP-3F-02	6.8	0.00610	795.2	44.7
CHAMP-3F-04	7.6	0.00504	1309.4	38.4
CHAMP-3F-05	5.0	0.00508	1181.8	26.3
CHAMP-3F-13	5.0	0.00434	1129.9	31.3
CHAMP-3M-01	10.6	0.00545	1480.6	29.2
CHAMP-3M-03	12.9	0.00486	1768.6	3.9
CHAMP-3M-07				
CHAMP-3M-08	2.4	0.00170	1529.9	31.4
CHAMP-3M-11	8.0	0.00625	1014.7	30.9
CHAMP-3M-14	7.5	0.00690	1348.2	38.1
CHAMP-3M-15	6.7	0.00538	1003.5	35.6
CHAMP-4F-01	5.4	0.00346	613.7	24.4

CHAMP-4M-02	5.1	0.012025	523.3	25.1
CHAMP-5M-01	6.3	0.00538	1310.8	32.3
CHAMP-5M-03	11.5	0.00572	1865.7	42.6

Table 14. FMD response for the CON group

Participant ID	Scaled FMD (%)	Normalized FMD (%FMD/SR^{AUC})	SR (s^{-1})	TTP (s)
CHAMP-6F-02	3.0	0.00587	730.2	30.6
CHAMP-6F-04	9.1	0.00394	2112.7	43.2
CHAMP-6F-07	17.6	0.00820	2099.8	37.1
CHAMP-6M-01	4.9	0.00597	1127.2	43.9
CHAMP-6M-03	6.3	0.03075	282.9	37.1
CHAMP-6M-05	9.8	0.00941	1224.1	43.9
CHAMP-6M-06	7.4	0.00843	1079.7	45.8
CHAMP-6M-08	8.1	0.01203	989.1	31.9
CHAMP-6M-09	5.7	0.00947	886.8	33.6

Table 15. Blood analyses for the CIC group

Participant ID	LDL (mmol/L)	HDL (mmol/L)	TC (mmol/L)	TG (mmol/L)	CRP (mg/L)
CHAMP-2F-02					0.35
CHAMP-2F-03					
CHAMP-2M-01					0.18
CHAMP-2M-05	1.86	0.98	3.22	0.83	0.31
CHAMP-2M-09					0.19
CHAMP-2F-08	3.49	0.99	5.64	2.53	0.08
CHAMP-3F-02	1.89	1.36	3.68	0.93	0.30
CHAMP-3F-04	2.41	1.34	4.08	0.71	0.84
CHAMP-3F-05	3.00	1.45	4.77	0.70	0.87
CHAMP-3F-13	2.58	1.42	4.32	0.69	0.30
CHAMP-3M-01	2.88	1.69	4.85	0.62	0.65
CHAMP-3M-03	2.25	1.22	3.8	0.71	
CHAMP-3M-07					0.86
CHAMP-3M-08	2.44	1.19	4.37	1.62	0.16
CHAMP-3M-11					0.50
CHAMP-3M-14	2.24	0.97	4.01	1.75	1.97
CHAMP-3M-15	2.09	0.83	4.05	2.47	0.12
CHAMP-4F-01	1.36	1.04	2.9	1.29	0.42

CHAMP-4M-02	2.77	1.43	4.42	0.49	0.04
CHAMP-5M-01					0.20
CHAMP-5M-03					0.94

Table 16. Blood analyses for the CON group

Participant ID	LDL (mmol/L)	HDL (mmol/L)	TC (mmol/L)	TG (mmol/L)	CRP (mg/L)
CHAMP-6F-02					
CHAMP-6F-04	2.12	1.16	3.61	0.71	0.78
CHAMP-6F-07	1.87	1.38	3.69	0.96	0.15
CHAMP-6M-01	2.77	0.82	4.03	0.96	0.40
CHAMP-6M-03	2.30	1.93	4.49	0.56	0.91
CHAMP-6M-05					
CHAMP-6M-06	2.38	0.88	3.67	0.90	0.15
CHAMP-6M-08	2.34	1.59	4.17	0.53	0.04
CHAMP-6M-09	3.04	1.22	5.11	1.85	

Appendix C – Statistical Analyses

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
AGE	.145	30	.108	.957	30	.258

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
AGE	1.00000	20	12.6555000	2.32353287	.51955774
	2.00000	7	13.0485714	2.00520513	.75789630

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
AGE	Equal variances assumed	.487	.492	-.398	25	.694	-.39307143	.98864471	-2.42922333	1.64308047
	Equal variances not assumed			-.428	12.119	.676	-.39307143	.91888359	-2.39296441	1.60682155

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
SBP	.133	29	.200	.970	29	.556
DBP	.126	29	.200*	.961	29	.353
MAP	.121	29	.200*	.928	29	.048

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean

SBP	1.00000	20	102.8000	9.07048	2.02822
	2.00000	9	108.4444	9.58007	3.19336

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
SBP	Equal variances assumed	.044	.836	-1.524	27	.139	-5.64444	3.70255	-13.24146	1.95257
	Equal variances not assumed			-1.492	14.746	.157	-5.64444	3.78302	-13.71987	2.43098

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
DBP	1.00000	20	59.3500	4.22119	.94389
	2.00000	9	59.2222	3.30824	1.10275

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
DBP	Equal variances assumed	2.081	.161	.080	27	.937	.12778	1.59455	-3.14398	3.39953
	Equal variances not assumed			.088	19.589	.931	.12778	1.45154	-2.90416	3.15972

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
BASELINEDIAMETER	.093	28	.200*	.980	28	.838

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
BASELINEDIAMETER	1.00000	19	2.7775	.41806	.09591
	2.00000	9	3.4409	.48785	.16262

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
BASELINEDIAMETER	Equal variances assumed	.789	.383	-3.720	26	.001	-.66346	.17833	-1.03003	-.29689
	Equal variances not assumed			-3.514	13.792	.004	-.66346	.18879	-1.06895	-.25796

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
ABSFMD	.148	28	.117	.837	28	.001

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
ABSFMD	1.00000	19	.2186842	.15994723	.03669441
	2.00000	9	.3223333	.10352777	.03450926

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ABSFMD	Equal variances assumed	.131	.720	-1.767	26	.089	-.10364912	.05865244	-.22421094	.01691269
	Equal variances not assumed			-2.058	23.159	.051	-.10364912	.05037230	-.20781255	.00051431

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
RELFMD	.101	28	.200*	.948	28	.173

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
RELFMD	1.00000	19	6.2111053	2.39128794	.54859908
	2.00000	9	9.5725556	3.66854897	1.22284966

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
RELFMD	Equal variances assumed	1.248	.274	-2.919	26	.007	-3.36145029	1.15164323	-5.72868686	-.99421373
	Equal variances not assumed			-2.508	11.340	.029	-3.36145029	1.34026946	-6.30060514	-.42229544

Tests of Between-Subjects Effects

Dependent Variable: RELFMD

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	69.279[a]	2	34.639	4.117	.028	.248
Intercept	39.594	1	39.594	4.706	.040	.158
AGE	.272	1	.272	.032	.859	.001
CONDITION	65.501	1	65.501	7.786	.010	.237
Error	210.323	25	8.413			
Total	1768.278	28				
Corrected Total	279.601	27				

a. R Squared = .248 (Adjusted R Squared = .188)

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
MAXSR	.135	27	.200*	.971	27	.632

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean

MAXSR	1.00000	18	1191.1444	371.89614	87.65676
	2.00000	9	1170.2778	597.85250	199.28417

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
MAXSR	Equal variances assumed	1.520	.229	.112	25	.912	20.86667	186.38018	-362.99049	404.72382
	Equal variances not assumed			.096	11.198	.925	20.86667	217.71056	-457.28031	499.01364

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
NORMFMD	.225	27	.001	.641	27	.000

a. Lilliefors Significance Correction

Ranks

	CONDITION	N	Mean Rank	Sum of Ranks
NORMFMD	1.00000	19	11.68	222.00
	2.00000	8	19.50	156.00
	Total	27		

Test Statistics[a]

	NORMFMD
Mann-Whitney U	32.000
Wilcoxon W	222.000
Z	-2.336
Asymp. Sig. (2-tailed)	.019
Exact Sig. [2*(1-tailed Sig.)]	.019[b]

a. Grouping Variable: CONDITION

b. Not corrected for ties.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
TIMETOPEAK	.229	30	.000	.821	30	.000

a. Lilliefors Significance Correction

Ranks

	CONDITION	N	Mean Rank	Sum of Ranks
TIMETOPEAK	1.00000	21	13.79	289.50
	2.00000	9	19.50	175.50
	Total	30		

Test Statistics[a]

	TIMETOPEAK
Mann-Whitney U	58.500
Wilcoxon W	289.500
Z	-1.630
Asymp. Sig. (2-tailed)	.103
Exact Sig. [2*(1-tailed Sig.)]	.104[b]

a. Grouping Variable: CONDITION

b. Not corrected for ties.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
IMT	.151	30	.080	.935	30	.066

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
IMT	1.00000	21	.4433662	.06427117	.01402512
	2.00000	9	.4103667	.05087775	.01695925

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
IMT	Equal variances assumed	.349	.559	1.364	28	.184	.03299952	.02420201	-.01657604	.08257509
	Equal variances not assumed			1.499	19.109	.150	.03299952	.02200727	-.01304441	.07904346

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
COMPLIANCE	.089	30	.200*	.971	30	.577

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
COMPLIANCE	1.00000	21	.1805357	.07531410	.01643488
	2.00000	9	.1895989	.04756382	.01585461

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
COMPLIANCE	Equal variances assumed	3.539	.070	-.332	28	.742	-.00906317	.02730765	-.06500035	.04687400
	Equal variances not assumed			-.397	23.552	.695	-.00906317	.02283580	-.05624144	.03811509

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
DISTENSIBILITY	.176	29	.021	.910	29	.017

a. Lilliefors Significance Correction

Ranks

	CONDITION	N	Mean Rank	Sum of Ranks
DISTENSIBILITY	1.00000	20	15.15	303.00
	2.00000	9	14.67	132.00
	Total	29		

Test Statistics[a]

	DISTENSIBILITY
Mann-Whitney U	87.000
Wilcoxon W	132.000
Z	-.141
Asymp. Sig. (2-tailed)	.888
Exact Sig. [2*(1-tailed Sig.)]	.908[b]

a. Grouping Variable: CONDITION

b. Not corrected for ties.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
PWV	.294	29	.000	.716	29	.000

a. Lilliefors Significance Correction

Ranks

	CONDITION	N	Mean Rank	Sum of Ranks
PWV	1.00000	20	14.65	293.00
	2.00000	9	15.78	142.00
	Total	29		

Test Statistics[a]

	PWV
Mann-Whitney U	83.000
Wilcoxon W	293.000
Z	-.330
Asymp. Sig. (2-tailed)	.741
Exact Sig. [2*(1-tailed Sig.)]	.764[b]

a. Grouping Variable: CONDITION

b. Not corrected for ties.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
CRP	.183	25	.030	.808	25	.000

a. Lilliefors Significance Correction

Ranks

	CONDITION	N	Mean Rank	Sum of Ranks
CRP	1.00000	19	13.42	255.00
	2.00000	6	11.67	70.00
	Total	25		

Test Statistics[a]

	CRP
Mann-Whitney U	49.000
Wilcoxon W	70.000
Z	-.509
Asymp. Sig. (2-tailed)	.611
Exact Sig. [2*(1-tailed Sig.)]	.642[b]

a. Grouping Variable: CONDITION

b. Not corrected for ties.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
BMI	.125	27	.200*	.954	27	.264

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
BMI	Equal variances assumed	2.395	.134	-.957	25	.348	-1.33684	1.39683	-4.21367	1.53998
	Equal variances not assumed			-1.110	18.931	.281	-1.33684	1.20471	-3.85896	1.18528

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
HEIGHT	.074	29	.200*	.992	29	.998

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
HEIGHT	1.00000	21	1.5712	.11915	.02600
	2.00000	8	1.6054	.12859	.04547

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
HEIGHT	Equal variances assumed	.132	.719	-.675	27	.505	-.03414	.05055	-.13786	.06959
	Equal variances not assumed			-.652	11.883	.527	-.03414	.05238	-.14838	.08010

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
WEIGHT	.113	29	.200*	.945	29	.137

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
WEIGHT	1.00000	21	50.0333	14.69843	3.20746
	2.00000	8	55.0625	9.16062	3.23877

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
WEIGHT	Equal variances assumed	1.485	.234	-.898	27	.377	-5.02917	5.60180	-16.52312	6.46478
	Equal variances not assumed			-1.103	20.547	.283	-5.02917	4.55823	-14.52127	4.46294

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
RHR	.113	29	.200*	.978	29	.795

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
RHR	1.00000	20	65.0500	9.53374	2.13181
	2.00000	9	62.2222	8.99691	2.99897

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
RHR	Equal variances assumed	.026	.874	.751	27	.459	2.82778	3.76415	-4.89563	10.55119
	Equal variances not assumed			.769	16.368	.453	2.82778	3.67946	-4.95811	10.61366

Ranks

	GROUP	N	Mean Rank
DISTENSIBILITY	JIA	10	14.45
	CON	9	14.67
	INFL	10	15.85
	Total	29	

Ranks

	GROUP	N	Mean Rank
DISTENSIBILITY	JIA	10	14.45
	CON	9	14.67
	INFL	10	15.85
	Total	29	

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
LDL	.121	20	.200*	.984	20	.972

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
LDL	1.00000	13	2.4046154	.55727933	.15456148

	2.00000	7	2.4028571	.39152328	.14798189

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
LDL	Equal variances assumed	.837	.372	.007	18	.994	.00175824	.23818775	-.49865566	.50217214
	Equal variances not assumed			.008	16.446	.994	.00175824	.21398105	-.45086453	.45438102

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
HDL	.104	20	.200*	.961	20	.561

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
HDL	1.00000	13	1.2238462	.25001795	.06934250
	2.00000	7	1.2828571	.39118258	.14785312

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
HDL	Equal variances assumed	1.487	.238	-.413	18	.684	-.05901099	.14272127	-.35885724	.24083526
	Equal variances not assumed			-.361	8.719	.726	-.05901099	.16330624	-.43025920	.31223722

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
TC	.098	20	.200*	.978	20	.899

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Group Statistics

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
TC	1.00000	13	4.1692308	.69691536	.19328954
	2.00000	7	4.1100000	.54381369	.20554226

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
TC	Equal variances assumed	.304	.588	.194	18	.848	.05923077	.30467846	-.58087493	.69933647
	Equal variances not assumed			.210	15.316	.836	.05923077	.28214972	-.54107983	.65954137

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
TG	.283	20	.000	.808	20	.001

a. Lilliefors Significance Correction

Ranks

	GROUP	N	Mean Rank	Sum of Ranks
TG	1.00000	13	10.85	141.00
	2.00000	7	9.86	69.00
	Total	20		

Test Statistics[a]

	TG
Mann-Whitney U	41.000
Wilcoxon W	69.000
Z	-.357
Asymp. Sig. (2-tailed)	.721

Exact Sig. [2*(1-tailed Sig.)]	.757[b]

a. Grouping Variable: GROUP

b. Not corrected for ties.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
MAXDIAMETER	.139	28	.179	.969	28	.553

a. Lilliefors Significance Correction

Group Statistics

	CONDITION	N	Mean	Std. Deviation	Std. Error Mean
MAXDIAMETER	1.00000	19	2.9703	.44034	.10102
	2.00000	9	3.7887	.50586	.16862

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
MAXDIAMETER	Equal variances assumed	.830	.371	-4.382	26	.000	-.81839	.18674	-1.20225	-.43454
	Equal variances not assumed			-4.163	13.973	.001	-.81839	.19657	-1.24006	-.39673

ANOVA

AGE

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	4.729	2	2.364	.465	.633
Within Groups	137.217	27	5.082		
Total	141.946	29			

ANOVA

BMI

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	81.290	2	40.645	4.796	.018
Within Groups	203.376	24	8.474		
Total	284.665	26			

Multiple Comparisons

Dependent Variable: BMI

Bonferroni

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	.50000000	1.38081347	1.000	-3.0537182	4.0537182
	3	3.87777778*	1.33751697	.024	.4354892	7.3200663
2	1	-.50000000	1.38081347	1.000	-4.0537182	3.0537182
	3	3.37777778	1.41449680	.075	-.2626292	7.0181847
3	1	-3.87777778*	1.33751697	.024	-7.3200663	-.4354892
	2	-3.37777778	1.41449680	.075	-7.0181847	.2626292

*. The mean difference is significant at the 0.05 level.

ANOVA

RHR

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	53.682	2	26.841	.294	.747
Within Groups	2370.456	26	91.171		
Total	2424.138	28			

ANOVA

SBP

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	220.851	2	110.425	1.280	.294

Within Groups	2329.449	27	86.276		
Total	2550.300	29			

ANOVA

DPB

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	6.575	2	3.287	.186	.831
Within Groups	476.792	27	17.659		
Total	483.367	29			

ANOVA

MAP

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	6.717	2	3.359	.089	.915
Within Groups	1021.449	27	37.831		
Total	1028.167	29			

ANOVA

CRP

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.632	2	.316	1.785	.191
Within Groups	3.896	22	.177		
Total	4.528	24			

ANOVA

BASELINEDIAMETER

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2.698	2	1.349	6.690	.005
Within Groups	5.040	25	.202		

Total	7.738	27			

Multiple Comparisons

Dependent Variable: BASELINEDIAMETER

Bonferroni

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	-.68465820*	.20630898	.008	-1.2140426	-.1552738
	3	-.04475558	.20630898	1.000	-.5741400	.4846288
2	1	.68465820*	.20630898	.008	.1552738	1.2140426
	3	.63990262*	.21166855	.017	.0967657	1.1830396
3	1	.04475558	.20630898	1.000	-.4846288	.5741400
	2	-.63990262*	.21166855	.017	-1.1830396	-.0967657

*. The mean difference is significant at the 0.05 level.

Tests of Between-Subjects Effects

Dependent Variable: LOGDIFF

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[b]
Corrected Model	.007[a]	3	.002	2.658	.071	.249	7.975	.575
Intercept	.008	1	.008	8.554	.007	.263	8.554	.801
LOGBASELINEDIAMETER	.001	1	.001	1.170	.290	.046	1.170	.180
GROUP	.007	2	.003	3.849	.036	.243	7.697	.641
Error	.021	24	.001					
Total	.194	28						
Corrected Total	.028	27						

a. R Squared = .249 (Adjusted R Squared = .156)

b. Computed using alpha = .05

Pairwise Comparisons

Dependent Variable: LOGDIFF

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
1	2	-.035*	.016	.037	-.068	-.002
	3	.008	.014	.541	-.020	.037
2	1	.035*	.016	.037	.002	.068
	3	.044*	.016	.012	.010	.077
3	1	-.008	.014	.541	-.037	.020
	2	-.044*	.016	.012	-.077	-.010

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

ANOVA

PEAKDIAMETER

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	4.094	2	2.047	9.247	.001
Within Groups	5.534	25	.221		
Total	9.628	27			

Multiple Comparisons

Dependent Variable: PEAKDIAMETER

Bonferroni

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
JIA	CON	-.83106667*	.21617465	.002	-1.3857662	-.2763671
	INFL	-.02675556	.21617465	1.000	-.5814551	.5279440
CON	JIA	.83106667*	.21617465	.002	.2763671	1.3857662
	INFL	.80431111*	.22179051	.004	.2352014	1.3734208
INFL	JIA	.02675556	.21617465	1.000	-.5279440	.5814551
	CON	-.80431111*	.22179051	.004	-1.3734208	-.2352014

*. The mean difference is significant at the 0.05 level.

ANOVA

ABSOLUTEFMD

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.086	2	.043	1.980	.159
Within Groups	.544	25	.022		
Total	.630	27			

ANOVA

RELFMD

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	61.696	2	30.848	3.518	.045
Within Groups	219.241	25	8.770		
Total	280.937	27			

Multiple Comparisons

Dependent Variable: RELFMD

Bonferroni

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
JIA	CON	-3.23325556	1.36065106	.076	-6.7246570	.2581459
	INFL	-.11947778	1.36065106	1.000	-3.6108792	3.3719237
CON	JIA	3.23325556	1.36065106	.076	-.2581459	6.7246570
	INFL	3.11377778	1.39599854	.105	-.4683245	6.6958801
INFL	JIA	.11947778	1.36065106	1.000	-3.3719237	3.6108792
	CON	-3.11377778	1.39599854	.105	-6.6958801	.4683245

ANOVA

SR

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	158666.729	2	79333.364	.377	.690
Within Groups	5054581.278	24	210607.553		
Total	5213248.007	26			

ANOVA

NORMFMD

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.000	2	.000	3.114	.063
Within Groups	.001	24	.000		
Total	.001	26			

ANOVA

TTP

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	236.215	2	118.107	.731	.490
Within Groups	4359.551	27	161.465		
Total	4595.766	29			

Kruskal-Wallis Test FOR DISTENSIBILITY

Ranks

	GROUP	N	Mean Rank
DISTENSIBILITY	JIA	10	14.45
	CON	9	14.67
	INFL	10	15.85
	Total	29	

Test Statistics[a,b]

	DISTENSIBILITY
Chi-Square	.155
df	2
Asymp. Sig.	.925

a. Kruskal Wallis Test

b. Grouping Variable: GROUP

Kruskal-Wallis Test

Ranks

	GROUP	N	Mean Rank
PWV	JIA	10	12.75
	CON	9	15.78
	INFL	10	16.55
	Total	29	

Test Statistics[a,b]

	PWV
Chi-Square	1.105
df	2
Asymp. Sig.	.576

a. Kruskal Wallis Test

b. Grouping Variable: GROUP

ANOVA

COMPLIANCE

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.003	2	.001	.311	.735
Within Groups	.129	27	.005		
Total	.132	29			

ANOVA

IMT

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.007	2	.004	.928	.408
Within Groups	.103	27	.004		
Total	.110	29			

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
LDL	Between Groups	.505	2	.253	1.037	.376
	Within Groups	4.141	17	.244		
	Total	4.646	19			
HDL	Between Groups	.152	2	.076	.843	.448
	Within Groups	1.532	17	.090		
	Total	1.684	19			
TC	Between Groups	.601	2	.301	.729	.497
	Within Groups	7.017	17	.413		
	Total	7.619	19			

Ranks

	GROUP	N	Mean Rank
TG	JIA	7	9.29
	CON	6	12.67
	INFL	7	9.86
	Total	20	

Test Statistics[a,b]

	TG
Chi-Square	1.187
df	2
Asymp. Sig.	.552

a. Kruskal Wallis Test

b. Grouping Variable: GROUP