



**IDENTIFICATION AND MODIFICATION OF CARDIOMETABOLIC DISEASE RISK
FACTORS IN SOUTH AFRICAN URBAN PRIMARY SCHOOL CHILDREN**

By

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ABSTRACT

The initial asymptomatic process of atherosclerosis is known to develop in childhood and is associated with increases in cardiometabolic disease (CMD) risk factors. Low physical activity (PA) levels and sedentary lifestyles have been identified as contributory factors to CMD. In addition, PA levels are known to influence the function of the cardiac autonomic nervous system (ANS), and are a possible mechanism for explaining the association between insufficient PA, morbidity and mortality. Consequently, it has been proposed that sufficient PA may enhance cardiac ANS activity in children. However, there is still a lack of consensus on the exact dosage of exercise required for optimal ANS adaptation.

This thesis aims to identify and modify the risk for CMD in urban primary school children. A cross-sectional study was performed to establish PA levels in South African primary school children. This was followed by a study that examined associations between individual CMD risk factors and altered ANS activity. The effect of two different exercise doses on CMD risk factors in overweight children was explored in a pilot study that lead to the quasi experimental study where the effectiveness of isocaloric exercise protocols on CMD risk factors and cardiac autonomic modulation in children were explored. Exercise interventions were set at either 65% to 70% of the maximum heart rate (MHR) in the moderate-intensity continuous training (MICT = 29) group or >80% MHR in the high-intensity interval training (HIIT = 29) group, or the interventions were combined in the alternate (ALT = 27) group. Heart rate variability (HRV) was used to measure cardiac ANS activity.

Overall, we found significant discrepancies in PA levels among gender, age and ethnic groups, raising important questions about population group equality in terms of access to participate in PA. The second cross-sectional study established strong associations between individual CMD risk factors and cardiac ANS activity. Lastly, the pilot study showed different cardiometabolic effects induced by moderate-intensity and vigorous-intensity. While the quasi experimental study demonstrated that both the magnitude and components of CMD risk factors and ANS relate to exercise intensity. When the effects of these interventions were examined, enhanced vagal activity (RMSSD, pNN50, SD1) seemed to be achieved through high-intensity interval training (HIIT), when compared with moderate-intensity continuous training (MICT). In conclusion, this thesis provides evidence that HIIT induces more superior cardioprotective effects in children than does MICT. The favourable outcomes of HIIT may have important clinical implications in regards to reducing the risk of developing CMD; however, studies that implement longer terms are required to confirm the findings.

Keywords: cardiometabolic risk factors, children, physical activity, exercise intensity, cardiac autonomic nervous system

LIST OF ABBREVIATIONS

ANS	Autonomic Nervous System
BMI	Body Mass Index
CMD	Cardiometabolic Disease
CVD	Cardiovascular Disease
CRP	C-reactive Protein
DBP	Diastolic Blood Pressure
GLUT4	Glucose transporter type 4
HDL	High Density Lipoprotein
HF	High Frequency-domain
HIIT	High-Intensity Interval Training
HRR	Heart Rate Reserve
HRV	Heart Rate Variability
LDL	Low Density Lipoprotein
LF	Low Frequency-domain
LF/HF	Ratio between Low and High Frequency
MICT	Moderate-Intensity Continuous Training
NCEP	National Cholesterol Education Program Expert Panel
NO	Nitric Oxide
PA	Physical Activity
PWV	Pulse Wave Velocity
RMSSD	Square root of the mean squared differences of successive R-R intervals
RSA	Respiratory sinus arrhythmia
SD	Standard deviation

SDNN	Standard deviation of R-R intervals
TG	Triglycerides
SBP	Systolic Blood Pressure
THR	Target Heart Rate
vWF	von Willebrand Factor
WHO	World Health Organization
WHR	Wait to Hip Ratio
WC	Waist Circumference

LIST OF PUBLICATIONS

1. van Biljon A. & Semple S. J. (2017). Modification of cardiometabolic disease risk factors in overweight children: An exploratory study of different exercise doses. *Journal of Physical Education and Sport*, 17(1), 41, 278 – 283, online ISSN: 2247 - 806X; p-ISSN: 2247 – 8051.
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3. van Biljon, A., McKune, A., DuBose, K., Kolanisi, U., & Semple, S. J. Cardiac autonomic function and its association with cardiometabolic disease risk factors in black South African children. (In Press: *Autonomic Neuroscience: Basic and Clinical*, Reference: AUTNEU_2018_97).
4. van Biljon, A., McKune, A., DuBose, K., Kolanisi, U., & Semple, S. J. Do short-term exercise interventions improve cardiometabolic risk factors in children? (In Press: *The Journal of Pediatrics*, Reference: 2018645R4).
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CONFERENCE PRESENTATIONS

1. International Society for Behavioral Nutrition and Physical Activity (ISBNPA). Modification of Cardiometabolic Disease Risk Factors in Primary School Children: A Pilot Study. University of Gent, Belgium, 22-25 May 2013.
2. eThekweni-University Research Symposium. Physical Inactivity Epidemic: The Tangible and Intangible Costs. International Convention Centre, Durban, 5-6 April 2016.
3. Student Society-led Symposium Evolution from Different Disciplines. The Obesity Epidemic: An Evolutionary Approach. Department of Zoology, University of Zululand, 6 May 2016.
4. Post Millennium Development Goals (MGD) Health conference 2016. Physical Activity Levels in Urban-Based South African Children: A Cross-Sectional Study of 7348 Participants. University of Venda, Thohoyandou, Limpopo, 22-23 June 2016.
5. Junior Public Health Association of South Africa (JuPHASA) Conference. Modifying Cardiometabolic Disease Risk Factors in Urban Primary School Children: Three Different Exercise Interventions. International Convention Centre East London. 19 - 22 September 2016.
6. Life through Movement International Conference (LTMIC 2016). Physical Activity Levels in Urban-Based South African Children: A Cross-Sectional Study of 7348 Participants. University of Pretoria, Gauteng, 6-8 October 2016.

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CHAPTER 1: INTRODUCTION

The prevalence of both cardiovascular disease (CVD) and type 2 diabetes mellitus (T2D) has achieved epidemic proportions, leading to the coining of the term cardiometabolic disease (CMD), which is also known as metabolic syndrome or syndrome X (Saklayen, 2018). CVD is the leading cause of mortality and morbidity worldwide and is estimated to be responsible for 17.3 million deaths (Naghavi et al., 2015), and T2D causes an additional 3.96 million deaths per year in adults (Roglic & Unwin, 2009). CMD is a condition characterised by the clustering of insulin resistance, hypertension, dyslipidaemia and central obesity – all of which increase the risk for developing both CVD and T2D (Rodríguez-Colón et al., 2015). The diagnosis of CMD is well established in adults with the International Diabetes Federation (IDF), estimating a 25% prevalence of CMD worldwide (O'Neill & O'Driscoll, 2015). However, the occurrence of CMD in children is less known, mostly because the relevant literature has provided 40 contested definitions (Huang, Prescott, Godfrey, & Davis, 2015). This encouraged paediatric research to determine how to assess or predict future CMD risk (Sovio et al., 2013). Most research in this area has investigated associations between individual CMD risk factors, anthropometric measurements (De Quadros, Gordia & Silva, 2017) and ethnicity (Messiah, Arheart, Lopez-Mitnik, Lipshultz, & Miller, 2013). A systematic review that included 31 studies observed that BMI, WC and WHR were strong predictors of clustered CMD risk factors in children (6-17.9 y) (De Quadros, Gordia & Silva, 2017). Messiah et al. (2013) found ethnic differences for waist circumference (WC) and high-density lipoprotein (HDL) cholesterol in American children (8-11 y). The study concluded that ethnic-specific paediatric prevention and treatment models should be developed for future onset of CMD. Furthermore, research has demonstrated that ethnicity affects both CMD risk factors (Cook, Auinger, Li, & Ford, 2008) and anthropometric measurements (Mirmohammadi et al., 2013), suggesting that ethnicity may play a major independent role in predicting CMD risk factors.

The clustering of CMD risk factors has been reported in children as young as 9 years old (Bugge, El-Naaman, McMurray, Froberg, & Andersen, 2013), and researchers have proposed that it coexists with alterations in the cardiac autonomic nervous system

(ANS) (Kaufman, Kaiser, Steinberger, Kelly, & Dengel, 2007). The ANS controls cardiac-muscle contractions, visceral activities and glandular functions of the body via the innervations of its two branches: the parasympathetic activity and sympathetic activity (Malpas, 2010; Mann, Zipes, Libby, & Bonow, 2014). Paediatric research in obesity has described cardiac ANS dysfunction as a withdrawal in parasympathetic activity (Gutin, Barbeau, Litaker, Ferguson, & Owens, 2000; Nagai & Moritani, 2004; Kaufman et al., 2007). A greater understanding of ANS and its association with CMD risk factors may provide insight into the prevention of CMD. Heart rate variability (HRV) is a noninvasive method used to assess the functioning of ANS and has been investigated in children (Xie et al., 2013; Farah, Ritti-Dias, Balagopal, Hill, & Prado, 2014; Mazurak et al., 2016). Moreover, it would be interesting to explore how the association between CMD risk and ANS would present in children from black ethnicities because the latter has been linked to higher rates of obesity, insulin resistance and blood pressure when compared with white children (Cook et al., 2008). Last, the findings of this may have important implications for early ethnic-specific identification of disease risk.

It is estimated that 6% to 10% of CVD and T2D diagnoses are due to low physical activity (PA) levels in adults (Lee et al., 2012). Similarly, low PA levels have been associated with the clustering of CMD risk factors in children (González, Fuentes & Márquez, 2017). Despite the adverse effects of low PA, global reports have indicated that children are still not meeting the recommended 60 minutes of moderate-to-vigorous PA guidelines (Zembura, Goldys & Nalecz, 2016; Sharif et al., 2016; Harrington et al., 2016; Burghard, de Jong, Vlieger, & Takken, 2018). The latter studies included the Netherlands, Poland, Malaysia and Ireland. Similarly, only half of South African children (6-18 y) met the recommended amount of PA guidelines (Uys et al., 2016). This urges a better understanding of the determinants of PA among children. A European study observed that regions can influence PA levels in children aged 2.0–10.9 years old (Konstabel et al., 2014). Socioeconomic differences were used to explain the findings of lower income regions, which participated less in PA than the higher income regions (Nazroo, 2003). The National Youth Risk Behaviour Survey (YRBS) observed similar discrepancies in PA across South African provinces and identified the KwaZulu-Natal

province as having the lowest prevalence of learners who had physical education on their school timetables (Reddy et al., 2010). This correlates to a South African study that described the socioeconomic status of KwaZulu-Natal, Eastern Cape and Limpopo as poor and rural, in comparison with the other provinces (Spaull, 2012). Less opportunities to partake in PA may explain some of the socioeconomic barriers to PA in schools (Eime, Charity, Harvey, & Payne, 2015). Moreover, differences in PA levels have been observed among different age groups (Nader, Bradley, Houts, McRitchie, & O'Brien, 2008), genders (Minnaar, Grant & Fletcher, 2016) and ethnicities (Konstabel et al., 2014). However, little is known about the influence of ethnicity, age and gender across all South African provinces. Furthermore, it has been estimated that if PA levels were increased, the life expectancy of the world's population would expand by 0.68 years (Lee et al., 2012). Thus, it is warranted to profile the PA levels of South African school children to determine the discrepancies (if any); doing so could lead to developing targeted interventions.

Exercise has the capacity to not only reduce traditional CMD risk factors (Sperlich et al., 2011; Racil et al., 2013; Racil et al., 2016; Dias et al., 2017) but also to improve the parasympathetic tone (Gutin et al., 2000; Nagai & Moritani, 2004; Lucini et al., 2013; Bond et al., 2015) in normal-weight, overweight and obese children. Despite this, the optimal intensity of exercise required to induce specific CMD alterations remains unclear (Kelley & Kelley, 2013). It has been suggested that 12 weeks of moderate-intensity continuous training (MICT) is effective for attenuating dyslipidaemia (total cholesterol, LDL, VLDL, HDL) and insulin levels in obese children (11 ± 1.0 y) (Zorba, Cengiz, & Karacabey, 2011). Similar results were found among 5-year-old children following 10 weeks of MICT. A significantly lower waist circumference (WC), body fat percentage and fat mass were reported in both obese and normal-weight children. However, the obese group was the only one to show significant reductions in systolic blood pressure (SBP) (Tan, Chen, Sui, Xue, & Wang, 2016). The authors concluded that MICT was a safe and effective method for reducing CMD risk factors in obese and normal-weight children. The research on MICT in children is limited, possibly because many studies referred to MICT interventions as only exercise interventions (Tan et al., 2016; Meyer, Kundt, Lenschow, Schuff-Werner, & Kienast, 2006; Kelly et al.,

2004; Barbeau et al., 2002) or PA interventions (Ischander et al., 2007; Farpour-Lambert et al., 2009; Martínez-Vizcaíno et al., 2014), rather than to indicate the intensity of these interventions, which made the literature search difficult. This is not the case for high-intensity interval training (HIIT) interventions, which have received much attention in paediatric exercise literature as an effective alternative for improving CMD risk factors (Weston et al., 2016; Racil et al., 2016; Sperlich et al., 2011; Racil et al., 2013; Dias et al., 2017). Despite the significant volume of literature on exercise interventions on reducing CMD in children, there is still no clear exercise protocol that will induce the optimal cardiometabolic health benefits. In addition, little research has explored HIIT in relation to MICT in the context of improving CMD risk factors.

1.1 AIMS AND OBJECTIVES OF THE THESIS

The overall objective of this thesis was to identify and then explore different exercise interventions that may modify the risk for CMD in children from South African urban based primary schools. The specific aims were to:

1. Provide a PA level profile of South African children
2. Screen CMD risk factors in South African children and explore associations between the risk factors with a focus on cardiac ANS functioning
3. Design, implement, and compare the efficacy of different exercise interventions on improving cardiometabolic health in South African children from the KwaZulu-Natal province.

1.2 RESEARCH HYPOTHESES

Research Hypothesis 1

Majority urban South African children aged 9-13 years will not meet the recommended physical activity levels.

Research Hypothesis 2

Cardiometabolic risk factors will be associated with cardiac ANS functioning among South African children.

Research Hypothesis 3

Participating in different exercise interventions will significantly improve specific cardiometabolic risk factors.

Null Hypothesis 1

Urban South African children aged 9-13 years old will meet the recommended physical activity levels.

Null Hypothesis 2

Cardiometabolic risk factors will not be associated with cardiac ANS functioning among South African children.

Null Hypothesis 3

There will be no differences in cardiometabolic risk factors after participating in different exercise interventions.

1.3 ORGANISATION OF THESIS

Chapter 1 of this thesis presents an overview of the increased risk of CMD in South African children. In addition, the chapter explains how CMD relates to physical inactivity and the role that PA plays as a treatment and prevention modality.

Chapter 2 presents literature on different aspects of CMD in children. Specifically, the review is organised around four topics: first, the burden of physical inactivity levels in children; second, CMD in children; third, pathogenesis of CMD; and fourth, PA interventions.

Chapters 3 to 7 include five papers produced by this thesis. Paper 1 generated evidence about gender, ethnicity, age and provincial profiles of PA levels in South African youth. Paper 2 determined the association between CMD risk factors and cardiac ANS in South African primary school children. The effect of two different exercise doses on CMD risk factors in overweight children was explored in Paper 3. Papers 4 and 5 investigated the effect of different isocaloric exercise interventions on CMD risk factors and cardiac ANS activity in South African primary school children.

The final chapter discusses the main findings of the five papers. It presents conclusions and suggests possible avenues for future research.

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CHAPTER 2: LITERATURE REVIEW

2.1 THE BURDEN OF PHYSICAL INACTIVITY LEVELS IN CHILDREN

The global burden of sedentary lifestyles has been compared to that of obesity and smoking. Indeed, evidence has shown that physical inactivity contributes to more than 5.3 million deaths worldwide (Lee et al., 2012). Report cards on physical activity (PA) for children and youth indicate a worldwide trend of children becoming less active (NPAPA, 2016; AHKA, 2016; 2016; Uys et al, 2016). Regional studies in South Africa have confirmed low PA levels among children. A descriptive study done in Port Elizabeth reported on subjective (interviews) and objective (accelerometers) measurements of PA levels and found that 45.5% children (9–12 y) did not meet recommended amounts of moderate-to-vigorous physical activity (MVPA) (Walter, 2011). A longitudinal study in the North-West province indicated that 16% of boys and 39% of girls were insufficiently active. The study employed the short form of the International Physical Activity Questionnaire (Toriola & Monyeki, 2012).

Low PA levels are partly responsible for the global obesity epidemic, with more than 42 million children (<5 y) classified as either overweight or obese (WHO, 2016). The Global Burden of Disease, on the basis of preliminary data from 2000 to 2013, has estimated that 268 million children (5–17 y) are overweight and 91 million will be obese by 2025 (Naghavi et al., 2015). According to the data, approximately 3.9 million of those children will be South African children (Lobstein & Jackson-Leach, 2016). Obesity, however, does not occur in isolation and is accompanied by cardiovascular and metabolic abnormalities—such as hypertension, dyslipidaemia and insulin resistance (Huang et al., 2015). The clustering of these risk factors is known as CMD (also known as metabolic syndrome).

2.2 CARDIOMETABOLIC DISEASE IN CHILDREN

Preventive guidelines for identifying CMD are important because of the associated adverse health outcomes (Huang et al., 2015). However, to date there is no consensus regarding the diagnosis of CMD: Over 40 different definitions exist in the relevant literature (Huang et al., 2015). In these definitions, the most cited criteria adapted for children and adolescents come from the following organisations: the International Diabetes Federation (IDF), the World Health Organization (WHO) and the National Cholesterol Education Program and Adult Treatment Panel III (NCEP-ATP III) (Silveira et al., 2013) (see Table 1). These criteria differ in terms of the number of risk factors, reference values and age groups. The IDF criterion defines CMD in children (10–16 y) with abdominal obesity and the presence of two or more clinical risk factors, and the NCEP-ATP III's guidelines are applied to 12- to 19-year-old children and require three or more risk factors (Zimmet, Alberti, Kaufman et al., 2007; NCEP, 2002).

Table 1. Diagnostic Criteria for Cardiometabolic Disease, Adapted for Children and Adolescents (Silveira et al., 2013)

Organisation/ Criteria	WHO	NCEP-ATP III (12–19 y)	IDF (10–16 y)
Diagnosis	Three or more risk factors	Three or more risk factors	Obesity and two or more risk factors
Obesity	BMI \geq 95th percentile	WC \geq 90th percentile	WC \geq 90th percentile
Glycaemic Homeostasis	Glucose intolerance Insulin resistance	FG \geq 110 mg/dL	FG \geq 100 mg/dL
Blood Pressure	SBP $>$ 95th percentile	SBP/DBP \geq 90th percentile	130/85 mmHg
Lipid Profile	TG $>$ 105 mg/dL for $<$ 10 y $>$ 136 mg/dL for \geq 10 y HDL $<$ 35 mg/dL TC $>$ 95th percentile	TG \geq 110 mg/dL HDL \leq 40 mg/dL	TG \geq 150 mg/dL HDL \leq 40 mg/dL

BMI: body mass index; WC: waist circumference; FG: fasting glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; HDL: high-density lipoprotein.

Cardiometabolic Disease Risk

CMD risk can be classified under traditional and nontraditional risk factors. Traditional risk factors include clinical factors (obesity, hyperglycaemia, insulin resistance, hypertension and dyslipidaemia) and behavioural factors (PA and cardiorespiratory fitness) (Després et al., 2008). However, nontraditional risk factors are identified as inflammatory markers, such as C-reactive protein, arterial stiffness and cardiac ANS dysfunction (Santos-Magalhaes et al., 2015).

The following section discusses traditional and nontraditional risk factors of CMD.

Traditional Risk Factors

Obesity Indicators (Waist Circumference, BMI)

Waist circumference (WC) and body mass index (BMI) are anthropometric parameters associated with an increased risk for CMD (Silveira et al., 2013). The IDF and NCEP-ATP III recommend that the 90th percentile for WC be used to define abdominal obesity in children. However, the WHO's guidelines suggest screening obesity with BMI at or greater than the 95th percentile.

Glycaemic Homeostasis

Hyperglycaemia [≥ 100 mg/dL (Zimmet, Alberti, Kaufman et al., 2007) and ≥ 110 mg/dL NCEP, 2002)] results from either abnormal insulin action or function. This is explained in detail later in the thesis. The WHO's criterion includes measurements of insulin resistance (WHO, 1999); however, the NCEP-ATP III's and the IDF's criteria do not (NCEP, 2002; Zimmet, Alberti, Kaufman et al., 2007).

Blood Pressure

An increase in blood pressure places stress on several target organs (kidneys, eyes, heart, blood vessels and the brain), and it is associated with target-organ lesions. Paediatric hypertension is defined as blood pressure at least in the 90th percentile

(NCEP, 2002) or a measurement of 130/85 mmHg (Zimmet, Alberti, Kaufman et al., 2007).

Lipid Profiles

CMD is linked with high triglycerides (IDF: ≥ 150 mg/dL and NCEP-ATP III: ≥ 110 mg/dL) and low high-density lipoprotein cholesterol (HDL-C ≤ 40 mg/dL) (Zimmet, Alberti, Kaufman et al., 2007; NCEP, 2002).

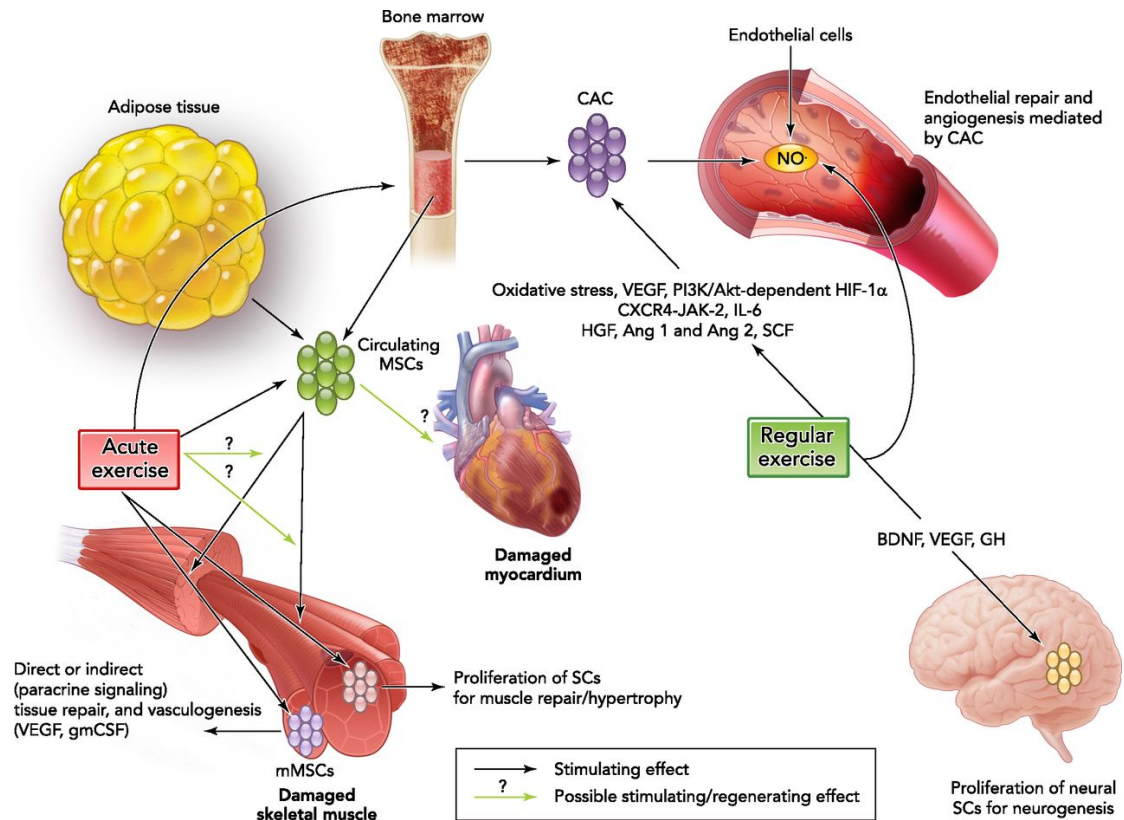
Physical Inactivity

Previous research has demonstrated that PA levels are associated with cardiometabolic risk in children (Ekelund et al., 2006). PA is a behaviour that can be measured either objectively with accelerometers (counts of activity per minute) and pedometers (count steps) or subjectively with questionnaires. However, no method is available to accurately quantify all dimensions (intensity, frequency and duration) of PA.

Cardiorespiratory fitness

An improvement in cardiorespiratory fitness (CRF) is a result of regular PA and has been suggested to be an independent risk factor for the development of CMD in children. Paediatric research has established inverse associations with CRF and BMI (Hsieh et al., 2014), obesity (Aires, Mendonça, & Silva, 2010), waist circumference (Ekelund et al., 2007), total cholesterol (Boreham & Riddoch, 2001), triglycerides (Ruiz et al., 2006), fasting glucose (Ekelund et al., 2007), blood pressure (Eisenmann, 2005) and CRP (Cesa et al., 2015).

Though PA and CRF are closely related, Steele, Brage, Corder, Wareham, and Ekelund (2008) have suggested that both influence cardiometabolic risk through separate pathways. When the day-to-day variability of PA is considered (Steele et al., 2008), it makes sense that the PA and CRF are measured differently and, consequently, have different effects because CRF remains more static. Figure 1 summarises the different effects.



CAC: circulating angiogenic cells; NO: nitric oxide; gmCSF: granulocyte macrophage colony stimulating factor; mMSCs: mobilising mesenchymal stem cells; SC: stem cells; VEGF: vascular endothelial growth factor; PI3K: phosphoinositide 3-kinase pathway; Akt-dependent HIF-1 α : protein kinase B hypoxia-inducible factor-1; CXCR4: hemokine receptor type 4; JAK-2: janus kinase 2; IL-6: interleukin 6; HGF: hepatocyte growth factor; Ang 1: angiotensin protein 1; Ang 2: angiotensin protein 1; SCF: stem cell factor.

Figure 1: Effects of acute exercise and regular exercise (Fiuza-Luces, Garatachea, Berger, & Lucia, 2013)

The main cardioprotective mechanisms of PA and CRF include macrophage-mediated reverse cholesterol transport, the capacity for vessel-wall regeneration and angiogenesis (production of new blood vessels) (Fiuza-Luces et al., 2013).

A single bout of exercise has been shown to provoke short-lived inflammatory responses through the following:

- Releasing vascular endothelial growth factor (VEGF) and granulocyte macrophage colony stimulating factor (gmCSF) (Fiuza-Luces et al., 2013)
- Mobilising mesenchymal stem cells (mMSCs) from bone marrow and adipose tissue that possess pluripotent progenitors (cells with the ability to

differentiate into many cell types) integral to the repair of damaged cells (Fiuza-Luces et al., 2013)

- Increased shear stress for the regulation of vascular tone (Fiuza-Luces et al., 2013) (previously discussed in thesis)

Regular exercise—that is, CRF—is associated with adaptive responses, including the proliferation of circulating angiogenic cells (CAC) (Fiuza-Luces et al., 2013). Exercise-induced proliferation of CAC is mediated through reducing CAC apoptosis (cell death) (Laufs et al., 2004) and oxidative stress (Witkowski, Jenkins, & Hagberg, 2011), stimulating the signalling pathways PI3K/Akt (via hypoxia-induced factor-1 α) (Cheng et al., 2010) and janus kinase-2 (via CXC motif receptor 4—CXCR4) (Xia et al., 2012), which are important for regulating cell growth and proliferation. Other factors associated with exercise-induced CAC proliferation include the stimulation of IL-6, hepatocyte growth factor (HGF), angiopoietin 1, angiopoietin 2 and stem cell factors (Bonsignore et al., 2010).

Nontraditional Risk Factors

Inflammatory Markers

Key inflammatory indicators that have been researched because of their association with atherosclerotic lesions include tumour necrosis factor alpha (TNF α), interleukin-6 (IL-6) and C-reactive protein (CRP). They are inflammatory markers associated with an increased risk (Arslan, Erdur, & Aydin, 2010).

CRP, predominantly produced by the liver, is an acute, prototypical phase reactant (24–48 h) that responds to pathogens and damaged cells. CRP promotes the removal of these cells by opsonisation and activating the classical complement pathway (C1q). A normal concentration of CRP in the general population is 0.8 mg/L; elevated levels range between 3 and 10 mg/L (Black, Kushner, & Samols, 2004). CRP is associated with body fat because of expressions of inflammatory cytokines in adipose tissue (Wellen & Hotamisligil, 2003). A clinical study that investigated the diagnostic value of CRP in 2,773 children reported that CRP < 5 mg/L ruled out serious infection,

thereby providing a guide for general practitioners to avoid hospital referrals (Verbakel et al., 2016). Early identification of elevated inflammatory markers is important to predicting children at risk for CMD.

Arterial Stiffness

Arterial stiffness (AS) refers to the loss of elasticity in arteries caused by structural changes within the arterial wall. AS has been associated with PA and CRF among children (Reed et al., 2005). Normal vascular function depends on the arteries' viscoelastic properties to maintain continuous blood flow. During the systolic phase, the left ventricle contracts to push blood into the aorta, and the aorta expands to accommodate the increase in blood volume and retains a portion of the stroke volume (see Figure 2). The aorta recoils during the diastolic phase, and the remaining stroke volume is propelled towards the periphery, maintaining continuous flow. This is known as the Windkessel effect and is accomplished by the compliancy (ability to expand and contract) of the arterial system, thereby allowing a continuous flow of blood (Izzo & Shykoff, 2001). Conversely, noncompliant arteries fail to regulate a continuous flow, leading to an increase in systolic blood pressure and a decrease in diastolic blood pressure. This increases the risk of damaging target organs during metabolic exchanges at the capillary level and is associated with atherosclerosis (Laurent & Boutouyrie, 2015).

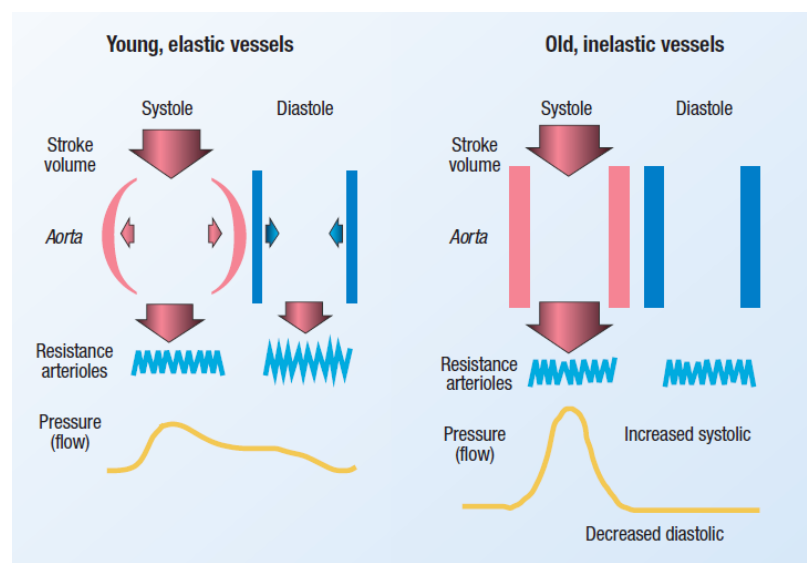


Figure 2: Aging and vascular function (Izzo & Shykoff, 2001).

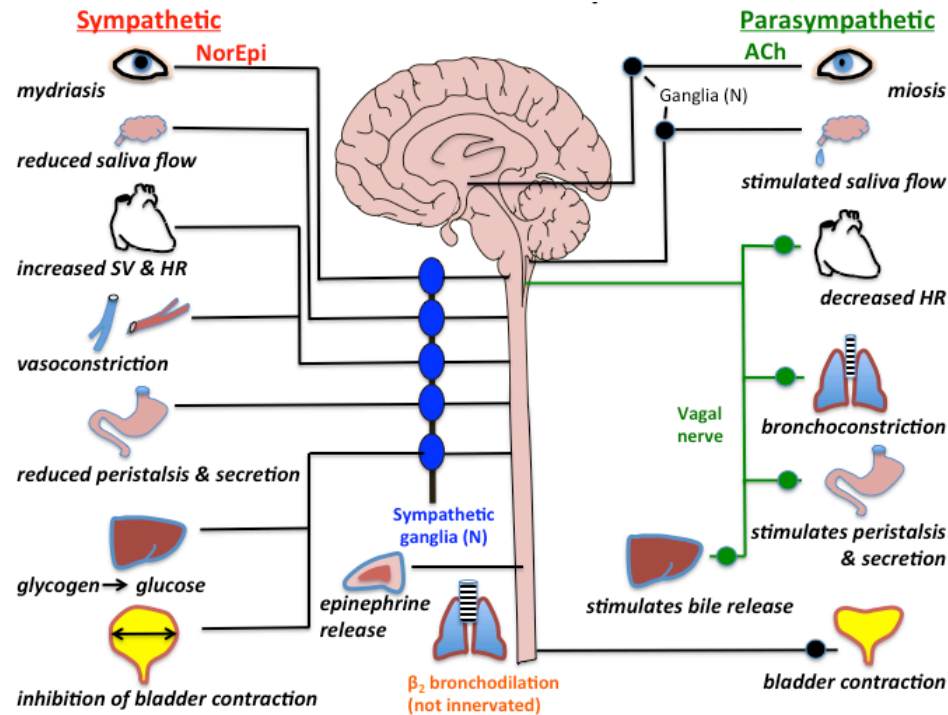
Arterial stiffness can be measured with pulse wave velocity (PWV), which is a noninvasive technique. PWV is more precise and reliable than other risk factors when the potential risk for developing cardiovascular diseases, stroke and diabetes is being predicted (Ribeiro et al., 2016; Tolezani et al., 2014). Physical inactivity is known to increase arterial tone and arterial stiffness (Zieman, Melenovsky & Kass, 2005); however, this has been shown to be reversible through increasing PA (Torrance, McGuire, Lewanczuk, & McGavock, 2007). Evidence suggests that regular PA reduces the clustering of traditional CMD risk factors, which in turn increases nitric oxide bioavailability, thereby improving endothelial vasodilation (Gielen, Schuler, & Adams, 2010). Furthermore, a lack of research exists on the relationship between arterial stiffness and PA among children.

Cardiac ANS Activity

The cardiac ANS controls the functioning of the heart. The effectiveness of the cardiac ANS is determined by the interplay between its two branches: the sympathetic nervous system and the parasympathetic (vagal) nervous system (Malpas, 2010). The parasympathetic (vagus) nerves release acetylcholine (ACh) that binds to cholinergic receptors, mostly muscarinic receptors, and induce different responses per the subtype of the receptor (Ulloa, 2005). For the purpose of this thesis, M_2 and M_3 are discussed. When ACh acts on M_2 , found on sinoatrial (SA) and atrioventricular (AV) nodes, cardiac inhibition is induced by hyperpolarising the cells (SA node) and lowering the conduction velocity (AV node), thereby decreasing heart rate. M_3 receptors located in endothelial cells produce vasodilation effects when binding to ACh by releasing nitric oxide (NO), thereby decreasing blood pressure (Ulloa, 2005).

In contrast, the sympathetic nervous system produces chronotropic (increases heart rate) and inotropic (increases contractility) effects on the heart, with epinephrine and norepinephrine interacting with adrenergic receptors (Malpas, 2010). The activation of the sympathetic nervous system and the withdrawal of parasympathetic activity is known as the flight-or-fight response. Exercise or environmental stressors trigger this response. The predominance of parasympathetic activity at rest is associated with cardiometabolic health, and chronic hypersympathetic activity or hypoparasympathetic

activity at rest have been linked to impaired ANS activity and thus CMD (Thayer, Yamamoto & Brosschot, 2010). See Figure 3 for a summary of the cardiac ANS and its different effects.



NorEpi: norepinephrine; Ach: acetylcholine.

Figure 3: Effects of the parasympathetic and sympathetic nervous systems (Medicine, Pharmacology and Nclex)

Heart rate variability (HRV) is a noninvasive technique used to measure cardiac ANS activity (Fukuba, 2009). The analysis of HRV comprises linear and nonlinear indices. A linear analysis includes time-domain and frequency-domain indices. A time-domain analysis reflects the magnitude of variability measured as the mean (IBI) and standard deviation (SDNN) in RR time intervals. High variability is believed to correspond to effective cardiac autonomic control (Porges, 2007). However, IBI and SDNN is limited in that it does not describe the dominant source of activity (vagal versus sympathetic). More precise time-domain assessments are calculated with the root mean square of differences between adjacent normal RR intervals (RMSSD), the count and percentage of adjacent RR intervals greater than 50 ms (NN50; pNN50). The latter is

entirely reflective of vagal tone: The higher RMSSD, NN50 and pNN50, the higher the vagal tone (Thayer et al., 2010).

A spectral analysis can provide information on the strength (power) of variance by filtering the sinus rhythm into bands by using the fast Fourier transform (FFT) or autoregressive (AR) spectrums. The very low frequency (VLF) band ranges between 0.0033 and 0.04 Hz and is considered to reflect the mechanism of sympathetic activity; however, research on VLF is lacking when compared with other power bands. Peaks between 0.04 and 0.15 Hz are associated with baroreflex activity modulated by both the parasympathetic and sympathetic nervous system and is defined as the low frequency (LF) band (Montano et al., 2009). Vagal activity is reflected at higher frequencies of 0.15–0.4 Hz in the high-frequency (HF) power band. The latter band is influenced by respiratory rates and is called the respiratory band because it corresponds to the variations in heart rate. This phenomenon is called respiratory sinus arrhythmia (RSA) (Karemaker, 2009). For example, during inspiration, the heart rate increases, and during expiration, it decreases. Last, the balance between the vagal and sympathetic activity can be estimated by calculating the LF (0.04–0.15 Hz) to HF (0.15–0.14 Hz) ratio (Thayer et al., 2010).

Using nonlinear data is a modern technique aimed at including multidimensional processes that control the cardiac system (quality, scaling and correlation properties) (Behbahani, Dabanloo & Nasrabadi, 2012). Moreover, nonlinear analyses can estimate the additional prognostic information on nonperiodic behaviour that exists within the RR intervals. This is done by plotting adjacent RR intervals on the Poincare plot. The first RR interval is presented on the x-axis and the second RR interval represents the y-axis. The parameters include standard deviation 1 (SD1), associated with vagal tone, and standard deviation 2 (SD2). SD1 is plotted perpendicular to the line and has been associated with parasympathetic activity. SD2 is plotted along the line and measures total variability (Seppälä et al., 2014).

Associations between HRV and PA, CRF, BP and adiposity have been established in children (Henje Blom, Olsson, Serlachius, Ericson, & Ingvar, 2009; Gutin et al., 2005; Farah, Ritti-Dias, Balagopal, Hill, & Prado, 2014). Blom et al. (2009) demonstrated significant correlations ($p < 0.05$) with PA and HRV among 99 healthy

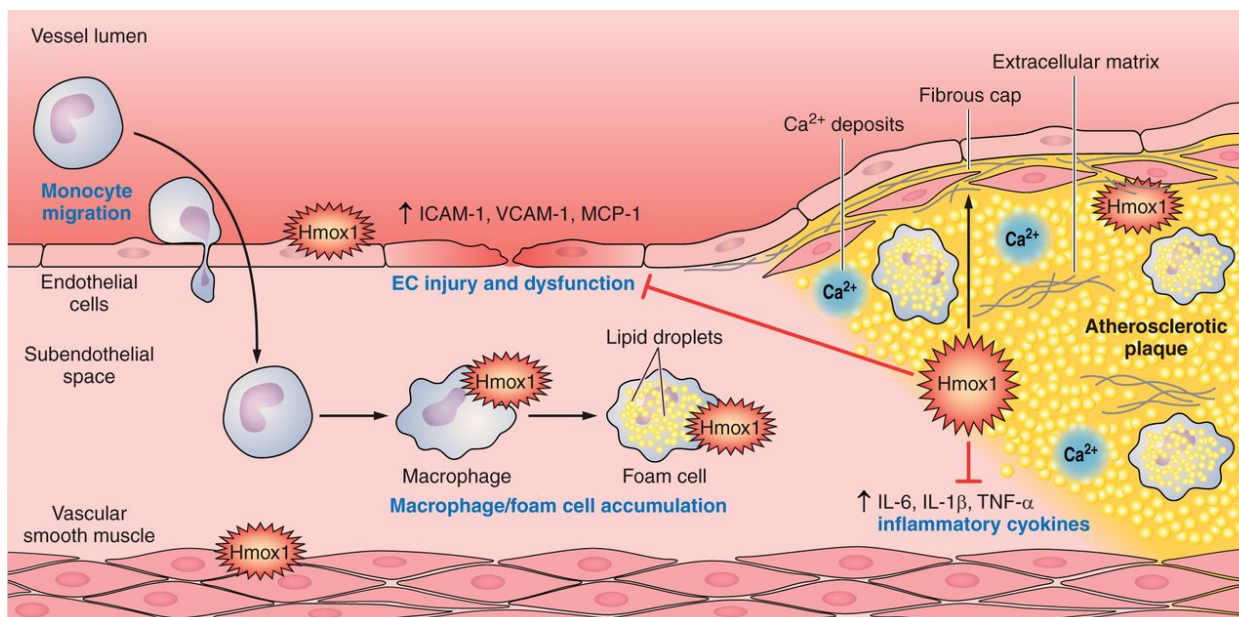
adolescents (15–17 y). Repeatable significant correlations were found for HF ($r = 0.26$, $r = 0.30$), LF ($r = 0.35$, $r = 0.29$) and SDNN ($r = 0.28$, $r = 0.37$) at baseline and after six months. Gutin et al. (2005) showed similar results with favourable HRV indices associated with higher PA levels among 304 adolescents. Moreover, higher adiposity, higher blood pressure and physical inactivity among 1,152 adolescent boys (16 y) were associated with greater sympathetic and lower parasympathetic modulations (Farah et al., 2014).

2.3 PATHOGENESIS OF CARDIOMETABOLIC DISEASE

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease characterised by lesions on the arterial wall. Atherosclerotic lesions can appear in foetal life as fatty streaks, and they may progress with time. In addition, they are influenced by risk factors such as obesity, hypertension, dyslipidaemia and physical inactivity (Plowman & Smith, 2013). In South Africa, 30% of the white children and 23.9% of the black children have an increased risk for developing atherosclerosis (Plowman & Smith, 2013).

Early stages of atherosclerosis are characterised by the accumulation of LDL-C, inflammatory cells, smooth muscle cells and fibrous elements in the subendothelium space (intima) (see Figure 4). Plasma concentrations exceeding the regulatory endocytic capacity of the cells result in LDL-C crossing the endothelium barrier and then being deposited in the intima. The LDL-C particles are then susceptible to oxidative stress through reactive oxygen species (ROS) present in the intima and become oxidised (oxLDL). The heme oxygenase-1 gene (HMOX1) responds to oxidative stress and induces expressions of cytokines, chemokines and adhesion molecules (monocyte chemoattractant molecule 1 (MCP-1), vascular cell adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule 1 (ICAM-1). This allows recruitment and transmigration of monocytes and lymphocytes across the endothelium (Eikendal et al., 2015).



ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; MCP-1: chemoattractant protein-1; Ca²⁺: calcium ions; Hmox1: heme oxygenase; IL-6: interleukin 6; IL-1: interleukin 1; TNF- α: tumor necrosis factor alpha.

Figure 4. Atherosclerotic lesions in the coronary arteries (Ayer et al., 2016)

The monocytes differentiate into macrophages that absorb oxLDL particles through the scavenger receptor pathway; however, macrophages cannot process oxLDL, and they continue to grow (from depositing greater amounts of oxLDL) until emigration from the plaque site is no longer possible. In addition, the enlarged macrophages rupture and trigger more monocytes, thereby contributing to the progression of inflammation. The engorged macrophages are called foam cells, and the accumulation thereof forms fatty streaks (von Hundelshausen & Weber, 2007).

The inflammatory response is amplified via T-cell (T lymphocytes) activation, which secretes tumour necrosis factor alpha (TNFα); this results in additional expressions of monocytes, adhesion molecules and cytokines. The inflammatory cytokine interleukin-6 (IL-6) stimulates the synthesis of CRP, which is a pattern-recognition molecule that binds to the ligand phosphocholine embedded in the oxLDL. CRP opsonises (a process that identifies the pathogen for ingestion) oxLDL after binding with the ligand by activating the classical complement pathway (C1q). This mediates further uptake of oxLDL by macrophages. Once CRP reacts with

macrophages, inflammation is suppressed via the inhibition of interleukin-1b (IL-1b) and interleukin-1ra (IL-1ra) (Eikendal et al., 2015).

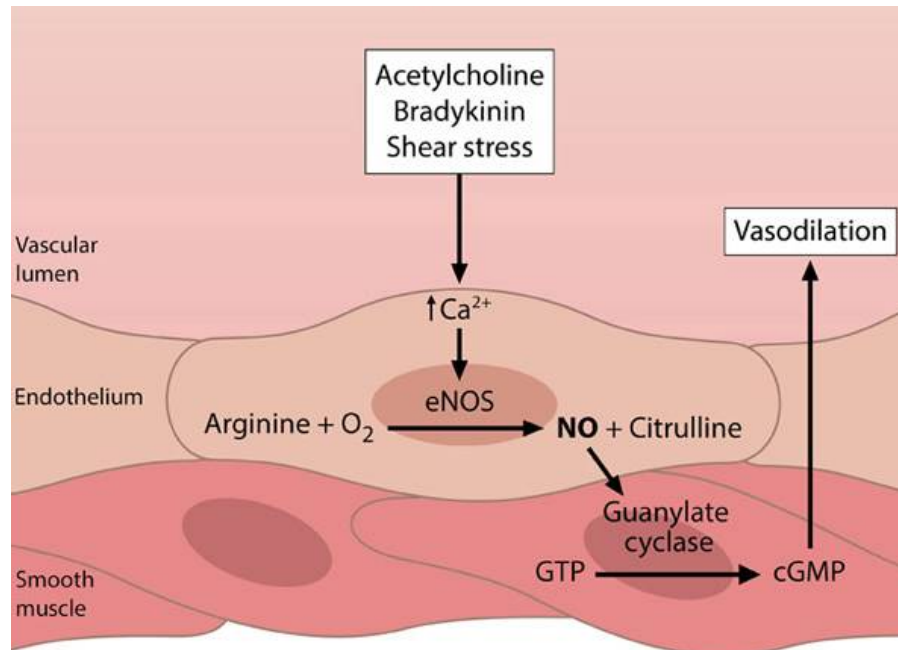
Atherosclerosis progresses further when smooth muscle cells migrate to and proliferate in the intima and then produce an extracellular matrix that forms a fibrous cap (collagen and elastin) that covers the foam cells. Macrophages continue to accumulate at the edges of the fibrous cap. This stage of the lesion has no clinical symptoms.

In the advanced stage of atherosclerosis, cytokines inhibit proliferation of smooth muscle cells and collagen production and induce the enzyme matrix metalloproteases (MMPs), which degrade the collagen, leading to a lesion prone to rupture (Heo et al., 2011). A ruptured lesion exposes the plaque to circulating blood, thereby initiating platelets to form a thrombus. Blood flow may be obstructed and cause myocardial infarction or a stroke if the thrombus occludes the vessel (Eikendal et al., 2015).

Endothelium Dysfunction

Endothelium dysfunction occurs in the early stages of atherosclerosis (explained above) and thus may already exist in children (Plowman & Smith, 2013). Hypertension, high blood glucose, physical inactivity and smoking are contributing risk factors of endothelium dysfunction (Hadi, Carr & Suwaidi, 2005).

An important antiatherosclerotic property in healthy endothelial cells is the ability to inhibit leukocyte adhesion to the vessel wall by releasing NO (Laxton et al., 2009). NO is evoked by acetylcholine, bradykinin and shear stress. When these bind to the receptors on the endothelium, calcium floods the insides of the cells. This activates an endothelium nitric oxide synthase (eNOS) concentration that forms NO from the amino acid L-arginine. NO diffuses into the vascular smooth muscle cell, where it activates the enzyme guanylyl cyclase, which in turn enhances the synthesis of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). cGMP causes the vascular smooth muscle to relax (Rybalkin, Yan, Bornfeldt, & Beavo, 2003). See Figure 5.



eNOS: endothelium nitric oxide synthase; NO: nitric oxide; cGMP: cyclic guanosine monophosphate; GTP: guanosine triphosphate; O₂: oxygen; Ca²⁺: calcium ions.

Figure 5: Endothelium-dependent vasodilation

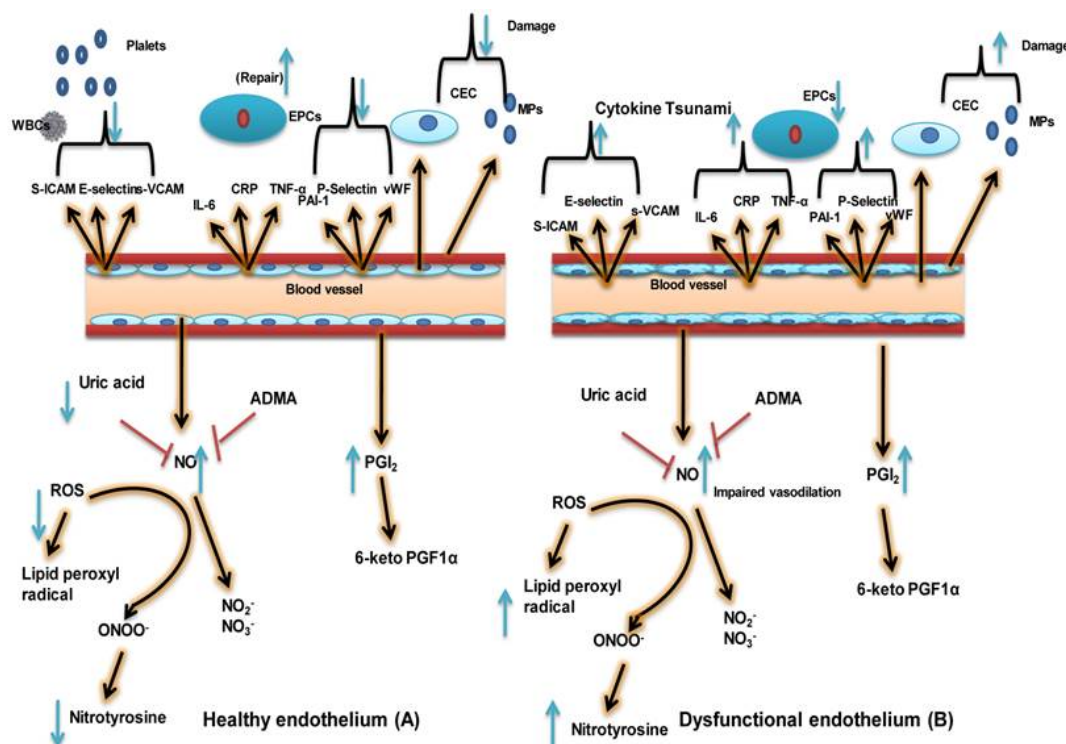
(from:<https://www.memorangapp.com/flashcards/129947/Amit%27s+Pharmacology/>)

The normal functioning of the endothelium depends on high levels of vasodilators (NO and prostacyclin) and endothelial progenitor cells (EPCs) and low levels of ROS, uric acid, leukocyte adhesion (VCAM, ICAM, P-selection and E-selection), CRP, IL-6, TNF- α , endothelial microparticles (EMPs) and circulating endothelial cells (CECs) (Bonomini, Tengattini, Fabiano, Bianchi, & Rezzani, 2008) (Figure 6).

Damaged endothelial cells produce excess ROS and reactive nitrogen species (RNS), leading to increased oxidative stress. ROS is generated as part of normal cellular metabolism and includes oxygen radicals—such as superoxide, hydroxyl radical, peroxy and alkoxy—as well as derivatives of oxygen with paired electrons (e.g., hydrogen peroxide and hypochlorous acid). ROS and RNS are derived not only from exogenous factors (e.g., air pollution and smoking) but also endogenous factors,

such as NADPH (nicotinamide adenine dinucleotide phosphate) oxidase (Moncada & Higgs, 2006).

ROS mediated lipid and protein peroxidation is associated with membrane dysfunction. Lipid peroxidation forms a lipid peroxyl radical that can further propagate the peroxidation process, and protein peroxidation causes the release of asymmetric dimethylarginine (ADMA) into the endothelium, thereby inhibiting NO synthesis (O'Donnell & Freeman, 2001).



ADMA: asymmetric dimethylarginine; NO: nitric oxide; eNOS: endothelial NO synthase; ROS: reactive oxygen species; WBCs: white blood cells; NO₂⁻: nitrogen dioxide; NO₃⁻: inorganic nitrate; ONOO⁻: peroxynitrite; PGI₂: prostacyclin; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; vWF: von Willebrand factor; PAI-1: plasminogen activator inhibitor 1; EPCs: endothelial progenitor cells; CEC: circulating endothelial cells; MPs: microparticles; s-VCAM: soluble vascular cellular adhesion molecule; s-ICAM: soluble intercellular adhesion molecule-1; CRP: c-reactive protein; PGI₂: 6-keto PGF1 α: 6-ketoprostaglandin factor 1 alpha.

Figure 6: Healthy endothelium versus dysfunctional endothelium (Burger & Rhian, 2012)

Furthermore, increased superoxide (due to excessive NADPH oxidase) reacts with existing NO generating peroxynitrite (ONOO⁻); this metabolism of NO leads to the formation of the oxidative byproducts nitrate (NO₃⁻) and nitrite (NO₂⁻) and has been

recognised as a marker of NO production in cellular tissues (Moncada & Higgs, 2006). Moreover, the production of NO from eNOS is also affected by the uncoupling of eNOS that produces superoxide due to insufficient amounts of L-arginine (Antoniades et al., 2009).

The reduced levels of NO stimulate the production of vasodilator prostacyclin (PGI_2) through prostacyclin synthase (PCS), generating the hydrolysed byproduct 6-Keto Prostaglandin $\text{F1}\alpha$ (6-k-PGF 1α). However, PGI_2 is short lived as the exposure of ONOO^- leads to the nitration of PCS, thereby impairing PGI_2 . Residues of nitrotyrosine are considered a marker of ONOO^- induced cellular damage (Galley & Webster, 2004).

This results in reduced vasodilation and increased proatherosclerotic activity through the expression of E-selection and P-selection, both of which allow the adhesion of VCAM, ICAM, PAI-1 (plasminogen activator inhibitor-1, thrombotic role) and vWF (von Willebrand factor) (Dong, Li, Yang, & Xu, 2014).

Insulin Resistance

Insulin resistance refers to an abnormal glucose homeostasis associated with CMD, physical inactivity, obesity, hypertension, subclinical inflammation and T2D (Berman, Weigensberg & Spruijt-Metz, 2012).

The pancreatic β cells secrete insulin in response to a rise in blood glucose (5 millimolar), and insulin binds to receptors on the liver, fat, muscle and blood vessel tissues, thereby lowering blood glucose levels by allowing glucose to enter cells for glycolysis or glycogen synthesis (Rask-Madsen & Kahn, 2012).

Defective receptors, insulin signalling and glucose transporters are the mechanisms underlying insulin resistance. Pancreatic β cells, neuron cells and vascular endothelial cells cannot regulate the transport of plasma glucose and are, therefore, more susceptible to hyperglycaemic damage (Röhling, Herder, Stemper, & Müssig, 2016). GLUT1 is a high-affinity, low-capacity glucose transporter with an estimated glucose K_m value of 1 mM; hence, the more glucose, the higher the activity of GLUT1 (upregulation). Interestingly, cancer cells contain GLUT1 expressions, which partly explains their rapid growth (Labak et al., 2016). The elevated intracellular glucose levels in these cells lead to increased glucose metabolism that exceeds mitochondrial

capacity, resulting in the formation of superoxide radicals (ROS). Oxidative stress occurs with the activation of protein kinase C (which increases endothelial cell permeability) and protein glycation (when glucose binds to protein) that results in the formation of advanced glycation end products (AGEs) (Ho, Chen & Bray, 2000). These events lead to endothelial damage and dysfunction.

Exercise has been shown to have an insulin-like effect by promoting the uptake of blood glucose in muscles cells without needing a signal from insulin. This is believed to occur via the contraction-mediated pathway (Ringseis, Eder, Mooren, & Krüger, 2015). Furthermore, according to the relevant literature, an increase in GLUT4 concentrations after exercise imply an increased insulin sensitivity (Roberts, Little & Thyfault, 2013).

2.4 PHYSICAL ACTIVITY INTERVENTIONS

PA prescription entails the manipulation of its four components: duration, intensity, frequency and type. PA volume incorporates duration and frequency variables, and it is measured in minutes per day or minutes per week. Intensity refers to the total effort exerted, and it is expressed as the total amount of energy expended (metabolic equivalents, or METs). Experiential research estimated METs with heart rate data and quantified intensity as a percentage of the heart rate reserve or a percentage of the heart rate max. Paediatric guidelines advocate moderate-to-vigorous intensity (USDHHS, 2008; WHO, 2010; Tremblay et al., 2011). The last variable of PA is the type or mode of activity; recommendations for children include aerobic, muscle and bone-strengthening activities. Paediatric guidelines (for 6–17 y) issued by the US Department of Health and Human Services (USDHHS) recommend 60 min of daily PA (USDHHS, 2008). This recommendation was claimed to improve cardiorespiratory and muscular fitness, bone health, and cardiovascular- and metabolic-health biomarkers (WHO, 2010). Controversial findings have revealed that complying to the recommended amount of PA is insufficient for modifying children's composite-cardiovascular risk scores and is limited to improving body composition and cardiorespiratory fitness (Füssénich et al., 2016). In addition, it should be noted that the PA guidelines are based on self-reported data, which have unique limitations (Janssen, 2007).

Some researchers have proposed that the health benefits of exercise stem from intensity rather than the duration of PA (Jakicic & Otto, 2006; Swain & Franklin, 2006). The results from 19 observational studies ($n = 12,815$) suggest that in children 5–19 years old, higher amounts of moderate-to-vigorous PA produce favourable cardiometabolic profiles than do lower amounts of moderate-to-vigorous PA. In those studies, the following cardiometabolic biomarkers were included: SBP, DBP, TG, TC, HDL, HOMA-IR, body fat, fasting glucose, fasting insulin, BMI, HRV, vascular function, waist circumference, insulin sensitivity, inflammatory markers (IL-6, CRP) and visceral adipose tissue (Gutin & Owens, 2011). Ten intervention studies ($n = 714$) showed favourable changes in biomarkers with 150–180 min/wk of moderate-to-vigorous PA in obese studies and 300 min/wk of moderate-to-vigorous PA as necessary in nonobese

studies. The biomarkers for these intervention studies included IL-6, CRP, insulin resistance, body fat percentage, BMI, waist circumference, SBP, DBP, TC, TG, FMD, IMT, LDL-C, apoA1, apo B and Lp(a) (Gutin & Owens, 2011).

The potent effects of vigorous PA have been demonstrated not only in traditional risk factors—such as improved insulin sensitivity (Racil et al., 2016), systolic blood pressure and aerobic capacity (García-Hermoso et al., 2016)—but also in novel risk factors, such as endothelial function and heart rate variability (Bond et al., 2015). The results of the European Youth Heart Study support the dose-response relation with PA intensity and cardiometabolic profiles in children (Andersen, Harro, & Sardinha, 2006). A cross-sectional study using accelerometers on 605 children (9–17 y) has indicated that minimal intensity and duration thresholds are required for reducing overweight status (>2000 cpm for >60 min) and SBP (>1500 cpm for 25 min). These counts per minutes (cpm) were classified as moderate PA (1500–6499 cpm). When vigorous PA (>6500 cpm) was performed, the required times were <10 min and <5 min to achieve the same results. Moreover, after the researchers adjusted for all of the PA intensities, the BMI z-score, waist circumference and SBP were decreased and VO_2 max increased with higher amounts of vigorous PA but not moderate or light PA (Hay, Maximova, & Durksen, 2012). The authors concluded that vigorous PA is superior to light and moderate PA for reducing CMD risk factors in youths.

Despite the evidence that supports the positive effects of high-intensity PA on children's cardiometabolic health, there is limited research on the exact protocol of high-intensity PA that will induce the most optimal effects on both traditional and nontraditional CMD risk factors.

Physical Activity Protocols That Reduce Traditional Cardiometabolic Disease Risk Factors

Several studies have examined the effect of different exercise dosages on reducing traditional CMD risk factors in children (Dalene et al., 2017; Ness et al., 2007; Davis et al., 2012; Lee, Yoo, & So, 2015; Logan, Harris, Duncan, & Schofield, 2014; Kelley & Kelley, 2007; Gutin et al., 2005; Kelly, Kelley, & Tran, 2003; Muthuri, Wachira, Onywera & Tremblay, 2015). The risk factors that were explored included resting blood

pressure, lipid profile (triglycerides, total cholesterol, LDL and HDL), hyperglycaemia, obesity indicators (BMI, WC, body fat percentage) and cardiorespiratory fitness. Moreover, it should be mentioned that most of these studies were conducted on overweight or obese children and adolescents.

Obesity Indicators

A systematic review and meta-analysis consisting of six studies ($n = 219$) examined the effects of exercise in overweight or obese children and showed a mean difference of -0.55 kg and -0.14 kg/m² in body weight and BMI, respectively. Exercise protocols ranged from 10 min to 75 min for 2 to 5 d/wk, at intensities of moderate physical activity (MPA) to moderate-to-vigorous physical activity (MVPA) (Dias, Green, Ingul, Pavey, & Coombes, 2015). A cross-sectional study revealed associations between different PA intensities, BMI and WC. The study showed favourable associations when sedentary time was substituted with MPA and vigorous physical activity (VPA), but unfavourable associations with low PA. More specifically, substituting 10 min/d with MPA was associated with improved WC (-0.32 to -0.47 cm; $p \leq 0.013$) in younger children (6–9 y), and VPA was required to induce the same in older children (9–15 y) (-1.08 to -1.79 cm; $p \leq 0.015$). Activity levels were defined as <100 cpm, 100–1999 cpm, 2000–5999 cpm and ≥ 6000 cpm for sedentary time, low PA, MPA and VPA, respectively. Furthermore, BMI showed similar associations with younger children responding to MPA and older children responding to VPA (Dalene et al., 2017). In a systematic review comprising 14 intervention studies on overweight and obese children and adolescents, improvements in body fat were observed with 155 to 180 min of MVPA per week (Atlantis, Barnes & Singh, 2006). Reductions in body weight were greater among exercise interventions that occurred over a longer period (weeks). Findings from a sample of 421 children (16 y) revealed vigorous intensity exercise to be a more significant predictor of body fat percentage when compared with MPA (Gutin et al., 2005). Similarly, a significant inverse relationship was established between fat mass and both total PA and MVPA in a cross-sectional study on a large cohort of 5,500 children (12 y) (Ness et al., 2007). However, when the researchers adjusted for MVPA, the associations between total PA and fat mass disappeared, and associations between

MVPA and fat mass remained significant. The authors concluded that PA intensity is more important than total PA.

Glycaemic Homeostasis

A study by Davis et al. (2012) demonstrated a dose-response relationship on insulin resistance, visceral fat and total body fat reduction among 222 overweight and obese children (7–11 y). Participants were randomly assigned to the 13-wk protocol of 5 d/wk, at 65% of VO_2 max and for 20-min or 40-min sessions. The high-dose protocol (40 min) revealed enhanced improvements in insulin sensitivity ($-3.98 \mu\text{U/mL}$; 95% CI, -7.04 to $-0.91 \mu\text{U/mL}$; $p = 0.01$), visceral fat (-24 cm^3 ; 95% CI, -32 to -15 cm^3 ; $p < 0.001$) and total body fat (-1.4% ; 95% CI, -2.2% to -0.7% ; $p < 0.001$) when compared with the low-dose group (20 min) (Davis et al., 2012). These findings suggest that higher volumes of exercise are required for improving insulin resistance, visceral fat and total body fat in obese children. Similarly, Nassis et al. (2005) revealed improved insulin sensitivity among 9- to 15-year-old overweight and obese girls following a 12-wk exercise training programme that comprised 40-min sessions, 3 d/wk, set at a target HR of ≥ 150 bpm. These results were achieved without changes in body weight or total adiposity. A 12-wk, high-intensity protocol that was conducted 3 d/wk at $\geq 80\%$ HRR (30-s sprint, 30-s recovery) with 10 adolescents with T2D (15.3 ± 2.2 y) resulted in significant improvements in body fat percentage, glycaemic control, endoplasmic reticulum stress and glucagon-like peptide-1 (Lee, Yoo, & So, 2015).

Blood Pressure

A systematic review on exercise prescription among obese children (10–17 y) showed reductions in BP. The exercise interventions were performed for 3–6 d/wk and comprised intensities ranging from 55% to 75% HRmax and lasting between 50 to 90 min (Farah, Berenguer, Prado, Júnior, & Dias, 2012). Similarly, Strong, Malina, and Blimkie (2005) suggested that an intensity of 80% HRmax is sufficient to reduce BP in hypertensive children. Leary et al. (2008) claimed that PA volume rather than intensity is primarily associated with improved BP profiles in children. The sample ($n = 5,505$) included 11- to 12-year-old children, with total PA recorded as 100 counts per minute

(cpm), and MVPA was defined as a value greater than 3600 cpm. After the researchers adjusted for potential confounders, the results revealed higher reductions in SBP (–0.42) and DBP (–0.40) in regard to total PA, when compared with the results of MVPA (SBP: –0.03 and DBP: –0.10). In contrast, a meta-analysis encompassing 12 studies showed no significant effects of exercise on BP among 1,266 overweight children (Kelly, Kelley & Tran, 2003). Interventions ranged between 8 and 36 wk and included 10- to 75-min sessions, occurring 2–5 d/wk. The study concluded that short-term exercise does not reduce BP in normotensive children and that further studies are needed in hypertensive children.

Lipid Profiles

In the context of lipid profiles, Escalante, Saavedra, García-Hermoso, and Domínguez (2012) reviewed seven studies that examined the effects of exercise on lipid profiles among obese children. The authors reported that exercise may reduce LDL by 35% and TG by 40%. The interventions comprised 60-min sessions at $\leq 75\%$ HRmax, 3 d/wk. Furthermore, combined exercises of ≥ 60 min at $> 75\%$ HRmax improved HDL concentrations by 25% (Escalante et al., 2012). This result is consistent with those of a meta-analysis conducted by Kelley and Kelley (2007), in which they reported that exercise reduced triglycerides by 12% in overweight and obese children.

Cardiorespiratory Fitness

A meta-analysis of 11 studies explored the cardiometabolic effects of different HIIT protocols ranging from 7 to 12 wk in adolescents (8–18 y) (Logan et al., 2014). Changes in aerobic fitness percentages ranged from +7.5% (Baquet, Berthoin, Gerbeaux, & van Praagh, 2001), +8.3% (Buchan, Ollis, & Thomas, 2011), +6.3% (Buchan et al., 2013), +10.9% (Koubaa et al., 2013), +7.6% (Racil et al., 2013) to +9.3% (Tjonna et al., 2009). Short intervention protocols (< 7 wk) ranged from the intervention of Baquet et al. (2001), which comprised maximal effort shuttle runs (10-s duration, repeated three times with 3-min rests, done once per week), to a 20-min multistage fitness test that was repeated up to six times in one session, 3 d/wk, by Buchan et al. (2013). The intervention of Racil et al. (2013) consisted of maximal shuttle runs

repeated eight times with 30 s of active recovery. An incremental increase in intensity was used by Koubaa et al. (2013): Participants ran at 80% VO₂ max, and the increment was increased by 5% every 4 wk. Tjonna et al. (2009) had intensities set at 90% to 95% HRmax, consisting of four sessions performed twice per week on treadmills.

These results provide sufficient evidence that small volumes of exercise reduce traditional risk factors among children, thus implying a reduced risk for developing CMD. However, reducing traditional risk factors with PA does not fully explain the magnitude of risk reduction. Some research has reported that 40% of the cardiovascular risk reduction through PA accounted for the direct effect of PA on the vascular wall (Mora, Cook, Buring, Ridker, & Lee, 2007; Green, Maiorana, O'Driscoll, & Taylor, 2004). Hence, there is a need to investigate different exercise protocols and their effects on reducing nontraditional risk factors.

Physical Activity Protocols That Reduce Nontraditional Cardiometabolic Disease Risk Factors

The effects of exercise on reducing nontraditional risk factors are not well understood, though it is believed that exercise-induced increases in shear stress (resulting from greater blood flow) reduce atherosclerotic risk via the release of nitric oxide in the endothelium (Green et al., 2004). This section investigates the effects of different exercise protocols on nontraditional CMD risk factors.

Inflammatory Markers

The effects of exercise on inflammatory markers are well documented in paediatric research (Rosa et al., 2011; Kamal & Ragy, 2012; Park et al., 2012). Intermittent training at 80% VO₂ max for 10 sets of 2-min cycling showed reductions in interleukin-6 (proinflammatory cytokines) and myeloperoxidase (enzyme present in neutrophils, macrophages and monocytes) in 47 obese children (12.7 ± 0.4 y) (Rosa et al., 2011). The authors hypothesised that higher concentrations of myeloperoxidase are indicative of lipid peroxidation and thus a marker of oxidative stress. Similarly, after 12 wk that included three sessions of 20–45 min each week at 60% to 65% HRR, Kamal and Ragy (2012) demonstrated significant reductions in CRP levels ($p < 0.05$) among

obese children ($n = 12$) with and without metabolic syndrome ($n = 32$). In addition, the study showed further significant reductions in BMI (47.4 kg/m^2 to 32.6%) and SBP (18.3 mmHg to 15.1%). The authors concluded that 12 wk of exercise may reduce multiple risk factors associated with metabolic syndrome in children. Another exercise study with a 12-wk duration showed increased concentrations of CD34+, CD133+ and CD34+/CD133+ cells. All of these were indicative of exercise-mobilising endothelial progenitor cells (EPC) that participate in vasculogenesis (new blood vessel formation); hence, they play an important role in the maintenance of vasculature (Park et al., 2012). The exercise protocol comprised 3 days in which aerobic exercise (50% to 70% HRR) and resistance training for 80 min were combined.

Arterial Stiffness

A 2007 review on the effectiveness of PA interventions in children reported that 40 min of MVPA for 3–5 d/wk was necessary to improve vascular function and to reduce blood pressure in obese children (Torrance et al., 2007). Using a sample of 99 children (9–11 y), Reed et al. (2005) determined the predictors of arterial compliance. The results revealed that children in the highest fitness quartile had a 34% greater compliance than children within the lower quartiles (Reed et al., 2005). Other predictors of arterial compliance included body mass, blood pressure, maturation and height. Similarly, the high-tertile PA group had significantly lower PWV and a higher brachial-artery dispensability when compared with the low- and middle-tertile PA group, among a total of 156 adolescents. Kelly et al. (2004) concluded that exercise may still improve endothelial function even with minimal changes in traditional cardiovascular risk factors. The study found significant improvements in $\text{VO}_2 \text{ max}$ (21.8 ± 2.1 to $23.2 \pm 1.5 \text{ mL/kg/min}$; $p < 0.05$), HDL (1.02 ± 0.03 to $1.10 \pm 0.04 \text{ mmol/L}$; $p < 0.05$) and flow-mediated dilation (FMD) (746 ± 66 to $919 \pm 94\%$ s; $p < 0.05$) among 25 overweight children ($10.9 \pm 0.4 \text{ y}$). Body weight and body composition remained unchanged after the 8-wk exercise protocol, which was set at 50% to 60% of $\text{VO}_2 \text{ max}$ for 30 min, four sets per week (Kelly et al., 2004). Thus, the results from these studies suggest that exercise interventions aimed at increasing CRF may be effective for reducing both arterial stiffness and BP.

Cardiac Autonomic Nervous System Activity

Regular PA is known to increase HRV indices in adults, and the available research on children suggests the same. Paediatric research has documented that HRV can improve with training protocols that range from 2 weeks to 12 months. Intervention studies have focused more attention on vigorous and moderate-to-vigorous exercise intensities (Mandigout et al., 2002; Gutin, Barbeau, Litaker, Ferguson, & Owens, 2000; Bond et al., 2015; Gamelin et al., 2009).

High-intensity protocols were performed by Mandigout et al. (2002), Bond et al. (2015) and Gamelin et al. (2009). Mandigout et al. (2002) showed increased effects on RR (887 ± 118 ms; $p < 0.05$), SDNN (120 ± 35 ms; $p < 0.05$), LF ($3.3 \pm 0.3 \log m^2$; $p < 0.01$), HF ($3.1 \pm 0.3 \log m^2$; $p < 0.05$) and total power ($3.7 \pm 0.3 m^2$; $p < 0.01$) among 19 children (10–11 y). The protocol involved three sets per week at $>80\%$ HRmax and lasted 13 wk. The 60-min sessions entailed combined sessions of interval training (10 x 100 m, 6 x 200 m and 4 x 600 m), continuous long-distance running (15–35 min) and aerobic activities (swimming, soccer and basketball) (Mandigout et al., 2002). Similarly, Bond et al. (2015) showed enhanced RMSSD among 13 adolescents (13–14 y) from a 2-wk HIIT protocol that consisted of six sessions of 8–10 x 1-min cycling at $90\% \text{VO}_2$ max, separated by 75 s of rest (Bond et al., 2015). Results revealed no effect on aerobic fitness or traditional CVD risk factors, as measured by triglycerides, cholesterol, glucose, insulin and BP. RMSSD improved from the 50th to 75th percentile cut-off points in adolescents after 1 day of the 2-wk HIIT ($p = 0.001$, $ES = 0.71$). RMSSD remained significant in the 75th percentile ($p = 0.02$, $ES = 0.44$) after 3 days of the intervention. The authors concluded that a single bout of HIIT may acutely promote RMSSD independent of improved traditional CVD risk factors.

On the other hand, no changes in HRV were observed in a sample of 38 children (9.3 ± 1 y) following 7 wk of 3 x 30 min running at maximum and supermaximum intensities (100% to 190% of MAV) (Gamelin et al., 2009). The authors concluded that the high exercise intensities might have caused fatigue among participants and hence did not affect the autonomic system.

In addition to these intervention studies, Gutin et al. (2000) demonstrated increased RMSSD (54–60 ms) in 79 obese children (7–11 y) after their participating in a 4-month MVPA (average of 157 bpm) programme for 40 min, 5 d/wk. The study also established significant ($p < 0.005$) baseline associations with higher RMSSD levels and lower levels of fat mass, fat-free mass, subcutaneous abdominal adipose tissue and resting HR (Gutin et al., 2000). Similarly, higher MVPA resulted in enhanced vagal activity (RMSSD: 49.2 ± 13.6 versus 38.1 ± 11.7 ms; $p = 0.006$) and lower SBP (107.3 ± 9.9 versus 112.9 ± 8.1 mmHg; $p = 0.046$) when compared with lower MVPA in 52 healthy adolescents (14.5 ± 0.7 y). MVPA was defined as 3000–5200 cpm and VPA as >5200 cpm. The study concluded that PA has an intensity-dependent effect on markers of cardiovascular health; more specifically, high volumes of MVPA favourably induced vagal activity ($\beta = 0.448$; $p = 0.010$) and systolic blood-pressure changes, whereas high volumes of VPA contributed to the maximum exercise capacity ($\beta = 0.248$; $p = 0.016$) (Radtke et al., 2012).

Moreover, Buchheit, Platat, Oujaa, and Simon (2007), using triaxial accelerometers, compared the effects of 210 min/wk of moderate PA with 60 min/wk of vigorous PA on HRV in 67 preadolescents (12 y). The study found that 60 min/wk of vigorous PA yielded more significant ($p < 0.05$) alternations in HRV (HF/LF + HF) than did 210 min/wk of moderate PA (Buchheit et al., 2007).

Last, the only moderate PA protocol available in paediatric literature was conducted in 2004 by Nagai and Moritani, their study included 305 children (6–11 y) that initially had low HRV values. The 12-month protocol produced heart rates between 130 and 140 bpm and lasted 20 min for 5 d/wk. The results showed significant increases in all of the frequency-domain components of HRV. However, the initially low HRV values might have contributed to the significant improvements, thereby placing a major limitation on the latter study's findings.

According to these findings, it appears that exercise can induce cardiac autonomic adaptations if the exercise protocol does not cause fatigue (lead to overtraining). However, the discrepancies in exercise prescription among paediatric studies contribute to the complexity of recommending specific exercises for achieving optimal cardiometabolic health in children. Considering the evidence that high-intensity

protocols positively affect traditional and novel risk factors, high-intensity protocols seem to be more suitable for modernised societies, where a lack of time is documented as the primary barrier to PA participation. This emphasises the need for future research to establish set protocols for VPA that will induce the most benefits in the least amount of time.

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CHAPTER 3: PAPER 1

Physical Activity Levels in Urban-Based South African Children: A Cross-Sectional Study of 7348 Participants

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3.1 ABSTRACT

Purpose This study investigated physical activity (PA) levels in urban-based South African primary school children. **Methods** Seven-thousand three-hundred and forty-eight ($n = 7348$) children (3867 males and 3481 females) aged 8-14 years completed the Physical Activity Questionnaire for Older Children (PAQ-C) between August and November 2012. Data were analyzed in 2013 to 2016. Participants were multiracial including: Caucasian (49%), Black (39%), and other ethnic groups (12%). Differences in PA levels by ethnic origin and province were determined using ANCOVA after adjusting for gender ($p < 0.05$). Bonferonni corrections controlled for multiple comparisons. A fitted regression model examined age related differences in PA adjusting for province. **Results** Fifty-seven percent ($n = 4224$) of South African children between 8-14 years old engaged in moderate PA levels. Thirty-one percent ($n = 2247$) of children did not meet international recommended amounts of moderate-to-vigorous physical activity (MVPA). Overall, males reported higher PA levels than females ($p < 0.0001$). PA levels declined with age from 11-14 years by 14% and 20% in males and females, respectively. Black children had greater PA levels when compared to Caucasian children ($p = 0.0039$). PA levels were significantly different across provinces ($p < 0.0001$). **Conclusion** This study provides evidence of the inequality in PA levels within gender, age, ethnic groups, and provinces. A targeted approach to promote PA levels among high-risk populations in South Africa is warranted. Increased PA levels will reduce the risk of chronic diseases and contribute to the health and growth of the country's economy.

Keywords: Physical activity, Urban Primary School Children

3.2 INTRODUCTION

Physical activity (PA) practices among South African school children are reported to be insufficient to promote health and prevent chronic diseases (Draper, Basset, de Villiers, Lambert, & HAKSA Writing Group, 2014). Results from South Africa's 2014 Report Card on Physical Activity for Children and Youth indicate that less than 50% children (6-18 yrs) meet recommended amounts of 60 minutes of moderate-to-vigorous PA (MVPA) (Draper et al., 2014). Low PA level is partly responsible for the obesity epidemic, threatening the economy and wellness of the South African population. Research indicates that 31.9% of South African children aged between 6 and 13 years old are overweight and 8.1% are obese (Armstrong, Lambert, Sharwood, & Lambert, 2006). A more recent study classified 15% - 25% of 9-10 year old South African children as overweight or obese (Kimani-Murage et al., 2010).

Major health care challenges are deemed to arise from populations that are physically inactive and it is reported that physical inactivity is the fourth leading risk factor contributing to global mortality (Lee et al., 2012). Physical inactivity may be responsible for 22% of ischaemic heart disease, 14% of type 2 diabetes mellitus, 16% of colon cancer, 11% of ischaemic stroke, and 10% of breast cancer (Joubert et al., 2007). In addition, several studies have shown a positive association between physical inactivity and health care costs (Wang, MacDonald, Reffitt, & Edington, 2005; Denking, Lukas, Herbolzheimer, Peter, & Nikolaus, 2012).

Establishing profiles of PA are critical for intervention research tackling the associated chronic diseases and avoiding healthcare costs. This study examined the prevalence of PA in South African children detailing differences between gender, ethnicity, age and region. Updating PA profiles of South African children may provide awareness around and contribute towards achieving the health-related Sustainable Development Goals for 2030 (Le Blanc, 2015).

3.3 METHODS

Participants

Seven-thousand three-hundred and forty-eight ($n = 7348$) South African children (3867 males and 3481 females) aged 8-14 years completed the Physical Activity Questionnaire for Older Children (PAQ-C) between August and November 2012. Data were analyzed in 2013 to 2016. The mean age was 11.14 ± 1.46 yrs. School principals in seven provinces (Gauteng, North-West, KwaZulu-Natal, Northern Cape, Western Cape, Eastern Cape, Mpumalanga) provided either written or verbal consent prior to participation. The participants included Caucasian ($n = 3634$), Black ($n = 2857$), and other ethnic groups ($n = 857$). The participants were predominantly Caucasian (49%) and Black (39%) and from the North-West (29%) and Gauteng (27%) provinces. For the purpose of the present study, we defined “urban area” as a locality characterized by a range of public and private service providers with a population of more than 15 000 inhabitants (Meyer, 2014; Statistics South Africa, 2011). The institution’s Research Ethics Committee provided ethical clearance for the study (UZREC171110-030).

Questionnaire

A modified version of the self-administered PAQ-C was used (Kowalski, Crocker, & Donen, 2004). The questionnaire measures general PA levels in children aged between 8 to 14 years old during a typical week in a school year. The survey includes 9-questions based on a broad spectrum of different activities taking place during physical education, first and second breaks, days and evenings and over the weekend. These questions were scored on a 5-point Likert rating scale assessing frequency and intensity of activities. A final mean score categorized children as having low, moderate, or high PA levels. Low levels of PA were from 1.00 - 2.33, moderate levels ranged from 2.34 - 3.66, and high levels ranged from 3.67 - 5.00 (Kowalski, Crocker, & Donen, 2004).

Demographic details including ethnicity and geographic location were added to the original questionnaire (gender and age were existing parameters on the questionnaire). The questionnaire was piloted using Survey Monkey on a convenient

sample prior to the main data collection; this sample did not form part of the final analysis.

The PAQ-C has demonstrated internal consistency among ethnicity groups (Moore, Hanes, Barbeau, Gutin, Trevino, & Yin, 2007) and acceptable test-retest reliability for males ($r = 0.75$) and for females ($r = 0.82$) (Crocker, Bailey, Faulkner, Kowalski, & McGrath, 1997). Convergent and construct validity of the PAQ-C had been established with moderate associations found between the activity rating scale ($r = 0.57$) and the 7-day PA recall interview ($r = 0.46$) (Kowalski, Crocker, & Faulkner, 1997).

Design and Sampling

This cross-sectional, descriptive survey study examined the PA levels across gender, ethnicity, provinces, and age groups. A two-stage cluster sampling design was utilized that allowed the selection of participants by province and age groups. Contact details for schools were from the online directory of South African schools (Directory of South African Schools). Schools, within all nine provinces were randomly selected from a published list of schools.

Data Collection

From the nine provinces that were contacted, seven provinces agreed to participate in the study. Participating schools from these provinces were requested to indicate an estimated number of eligible participants (8–14 yrs) enrolled within their school. The required number of questionnaires were delivered by courier and administered in class during school hours. The front page of the questionnaire contained short bullet point instructions on how to complete the questions and informed participants that there were no wrong answers. Questionnaires were collated according to province and not by the individual schools. Seven-thousand four-hundred and eighty-five (7485) questionnaires were returned of which 137 responses were incomplete or had missing values; these were excluded from the study. The final sample included 7348 participants.

Data Analysis

Means, standard deviation, frequencies and 95% confidence intervals (CI) were calculated for the final sample by ethnic group, gender, age and province. An independent t-test compared PA among gender ($p < 0.05$). Differences in PA levels by ethnic origin and province were determined via analysis of covariance (ANCOVA) after adjusting for gender ($p < 0.05$). Bonferroni corrections ($p < 0.05/3 = 0.0167$; $p < 0.05/7 = 0.00714$, respectively) were used for post hoc analysis when necessary. Finally, a fitted regression model estimated differences across PA levels by age, adjusting for province. The regression analysis was adjusted for province due to PA levels and age being statistically different by province. All data analyses were performed using SAS version 9.3.

3.4 RESULTS

Physical activity questionnaire for older children (PAQ-C) scores are presented in Table 1. The mean PAQ-C score of the total sample was 2.75 ± 0.73 . Males were significantly more active and recorded a mean score of 2.85 (95% CI: 2.82 - 2.87) compared with females that logged a mean of 2.64 (95% CI: 2.61 - 2.66) ($p < 0.0001$). All ethnic comparisons were statistically different ($p < 0.0001$). Bonferroni corrections ($p < 0.05/3 = 0.0167$) demonstrated higher PA levels in Black children compared with both Caucasian ($p = 0.0039$) and other ethnic group ($p < 0.0001$) children. The latter group ($p < 0.0001$) was less active compared with their Caucasian counterparts.

Table 1. Physical Activity Questionnaire for Older Children (PAQ-C) Scores by Gender, Ethnic Group, Age and Province

VARIABLE	N = 7348	PAQ-C SCORES MEAN ± SD	95% CI	P
GENDER				
M	3867	2.85 ± 0.75	2.82 - 2.87	< 0.0001 ^a
F	3481	2.64 ± 0.69	2.61 - 2.66	
ETHNIC GROUP				
B	2857	2.80 ± 0.74	2.77 - 2.82	< 0.0001 ^b
C	3634	2.75 ± 0.72	2.72 - 2.77	
O	857	2.59 ± 0.73	2.55 - 2.64	

AGE (YRS)			
8	144	2.46 ± 0.64	2.35 - 2.56
9	974	2.78 ± 0.77	2.74 - 2.83
10	1657	2.77 ± 0.72	2.73 - 2.80
11	1307	2.85 ± 0.78	2.81 - 2.90
12	1724	2.80 ± 0.71	2.77 - 2.84
13	1315	2.60 ± 0.67	2.56 - 2.64
14	227	2.43 ± 0.69	2.34 - 2.52
PROVINCE			
GT	2016	2.97 ± 0.73	2.94 - 3.00
NW	2113	2.70 ± 0.74	2.67 - 2.73
KZN	629	2.91 ± 0.68	2.85 - 2.96
NC	805	2.37 ± 0.64	2.33 - 2.42
WC	619	2.88 ± 0.71	2.82 - 2.93
EC	716	2.55 ± 0.68	2.50 - 2.60
MP	450	2.55 ± 0.62	2.49 - 2.61

PAQ-C: physical activity questionnaire for older children; M: male; F: female; SD: standard deviation; 95% CI: confidence interval; B: Black; C: Caucasian; O: Other ethnic groups; GT: Gauteng; NW: North-West; KZN: KwaZulu-Natal; NC: Northern Cape; WC: Western Cape; EC: Eastern Cape; MP: Mpumalanga; ^at-test; ^bANCOVA; ^cRegression Model.

Among the seven selected provinces, Gauteng participants recorded a mean PAQ-C score of 2.97 (95% CI: 2.94 - 3.00) and had significantly higher levels of PA compared with North-West ($p < 0.0001$), Northern Cape ($p < 0.0001$), Mpumalanga ($p < 0.0001$), Western Cape ($p < 0.0014$) and Eastern Cape ($p < 0.0001$). KwaZulu-Natal province had slightly lower PA levels compared with Gauteng (2.91 vs. 2.97) although, no significant differences were reported ($p = 0.0235$) with deflated alpha values ($p < 0.05/7 = 0.00714$). Northern Cape respondents had significantly lower levels of PA across all provinces [Gauteng ($p < 0.0001$), North-West ($p < 0.0001$), Western Cape ($p < 0.0001$), Mpumalanga ($p < 0.0001$), KwaZulu-Natal ($p < 0.0001$) and Eastern Cape ($p = 0.0005$)]. KwaZulu-Natal held the second highest PAQ-C score (2.91 ± 0.68) but was not statistically different from Western Cape (2.88 ± 0.71) ($p = 0.44$).

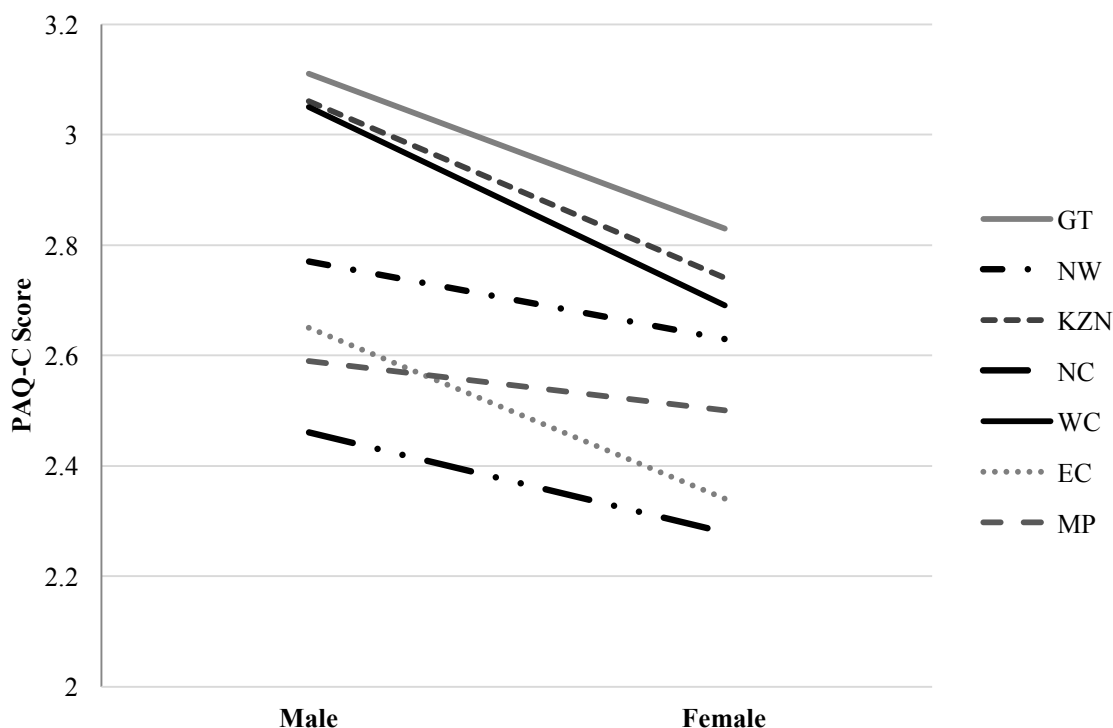
Gender characteristics are described in Table 2. From the 7348 participants, 53% were male and 47% female. Males ($n = 3867$) were mostly Caucasian (50%) and Black (39%) with a mean age of 11.14 ± 0.75 yrs and the majority resided in the North-West (28%) and Gauteng (25%) provinces. Females ($n = 3481$) had a mean age of 11.13 ± 0.69 yrs and consisted of 39% Black and 49% Caucasian respondents with 30% residing in Gauteng and 30% in North-West provinces.

Table 2. Physical Activity Questionnaire for Older Children (PAQ-C) Scores by Gender-Ethnic group, Age and Province

VARIABLE	MALES (N = 3867)			FEMALES (N = 3481)		
	N	PAQ-C Scores Mean \pm SD	95% CI	N	PAQ-C Scores Mean \pm SD	95% CI
ETHNIC GROUP						
B	1502	2.89 \pm 0.74	2.85 - 2.93	1355	2.69 \pm 0.73	2.65 - 2.73
C	1941	2.84 \pm 0.75	2.81 - 2.87	1693	2.64 \pm 0.67	2.60 - 2.67
O	424	2.73 \pm 0.77	2.66 - 2.80	433	2.46 \pm 0.67	2.40 - 2.53
AGE (YRS)						
8	82	2.53 \pm 0.65	2.39 - 2.67	62	2.37 \pm 0.63	2.21 - 2.53
9	484	2.82 \pm 0.78	2.75 - 2.89	490	2.74 \pm 0.76	2.68 - 2.81
10	835	2.85 \pm 0.75	2.80 - 2.90	822	2.69 \pm 0.67	2.64 - 2.73
11	842	2.98 \pm 0.78	2.93 - 3.04	465	2.62 \pm 0.73	2.55 - 2.69
12	792	2.93 \pm 0.71	2.88 - 2.98	932	2.69 \pm 0.69	2.65 - 2.74
13	694	2.68 \pm 0.70	2.63 - 2.74	621	2.51 \pm 0.62	2.46 - 2.56
14	138	2.59 \pm 0.68	2.48 - 2.71	89	2.18 \pm 0.63	2.05 - 2.31
PROVINCE						
GT	981	3.11 \pm 0.71	3.10 - 3.12	1035	2.83 \pm 0.72	2.78 - 2.87
NW	1083	2.77 \pm 0.78	2.73 - 2.82	1030	2.63 \pm 0.68	2.58 - 2.67
KZN	324	3.06 \pm 0.71	2.98 - 3.13	305	2.74 \pm 0.62	2.67 - 2.81
NC	420	2.46 \pm 0.66	2.40 - 2.52	385	2.28 \pm 0.61	2.22 - 2.34
WC	321	3.05 \pm 0.75	2.97 - 3.14	298	2.69 \pm 0.61	2.62 - 2.75
EC	484	2.65 \pm 0.65	2.59 - 2.71	232	2.34 \pm 0.68	2.25 - 2.43
MP	254	2.59 \pm 0.63	2.51 - 2.67	196	2.50 \pm 0.61	2.41 - 2.59

PAQ-C: physical activity questionnaire for older children; M: male F: female; SD standard deviation; 95% CI: confidence interval; B: Black; C: Caucasian; O: Other ethnic groups; GT: Gauteng; NW: North-West; KZN: KwaZulu-Natal; NC: Northern Cape; WC: Western Cape; EC: Eastern Cape; MP: Mpumalanga; *low levels of PA (1.00 - 2.33)

Province and gender interactions were significant ($p = 0.0002$) with a trend of males being more active compared with their female counterparts across all provinces (Figure 1). Gauteng males (3.11 ± 0.71) and females (2.83 ± 0.72) were 23% and 22% more active compared with Northern Cape males (2.46 ± 0.66) and females (2.28 ± 0.61), respectively. Western Cape demonstrated the largest gender difference with males (3.05 ± 0.75) 13% more active compared with females (2.69 ± 0.61) of that province.



PAQ-C: physical activity questionnaire for older children; GT: Gauteng; NW: North-West; KZN: KwaZulu-Natal; NC: Northern Cape; WC: Western Cape; EC: Eastern Cape; MP: Mpumalanga.

Figure 1. Physical Activity Questionnaire for Older Children (PAQ-C) Scores by Province and Gender

3.5 DISCUSSION

The primary findings of the study indicate significant differences in PA levels among gender, ethnic origin, age group and provinces. Males had higher PA levels compared with females ($p < 0.0001$), Black and Caucasian children were significantly more active than other ethnic groups ($p < 0.0001$), younger children tended to be more active than older children ($p < 0.0001$), and Gauteng province had greater PA levels compared with other provinces ($p < 0.0001$), but were not significantly different to KwaZulu-Natal province ($p = 0.0235$).

PA levels in the present study are in line with previous pediatric studies (Minnaar, Grant, & Fletcher, 2016; Mcveigh, & Meiring, 2014). Social and cultural explanations for

these PA level finding have been put forward. For instance, female participation in vigorous activities is not encouraged or praised by society compared with males and some cultures hold stronger values for sport participation than other cultures (Sallis, Zakarian, Hovell, Hofstetter, 1996; Belcher et al., 2010). A recent cross sectional study (n = 78) revealed that rural South African males aged 9–11 and 12–14 years recorded significantly more steps of 27.7% and 27.5% compared with females of the same age (Minnaar et al., 2016). A larger urban-based study (n = 767) found that South African males between the ages of 5-18 years old accumulated more MVPA per week when compared with their female counterparts (Mcveigh & Meiring, 2014). The results of the current study support and confirm gender differences in PA levels among South African children.

The trend of PA levels declining with age has been ascribed to biological maturation in terms of the onset and rate of puberty (Belcher et al., 2010; Bacil et al., 2015). Specifically, research has demonstrated a decline in PA levels with age, particularly in adolescent females (Nader, Bradley, Houts, McRitchie, & O'Brien, 2008; Troiano et al., 2008). However, conflicting results were found in a 10-year longitudinal Norwegian study that tracked PA levels in 630 children from age 13 (Kjønniksen, Torsheim, & Wold, 2008). Multivariate analysis indicated greater annual declines in males ($B = -0.17$) than in females ($B = -0.09$). The study speculated that sport participation had increased among females after the second century with the implementation of Title IX that provided increased opportunities for females to play sports. The current study show PA levels declining at an earlier age in females compared with males (10 yrs vs. 13 yrs) proving further explanation for the findings in the Norwegian study where participants were tracked from age 13. Belcher et al. (2010) recognized that 6 to 11 year old American children spent significantly more time in MVPA than older children aged 12-15 years (88 min/day vs. 33 min/day). Similarly, an Australian study that comprised of 6024 children aged 10 to 18 years old reported that older children were less active compared with younger children and that sedentary time peaked at 14 to 15 years old (Olds et al., 2009). Likewise, in the South of India, PA decreased significantly over 1 year amongst children aged 8 to 15 years old (Swaminathan, Selvam, Thomas, Kurpad, & Vaz, 2011).

The results of the present study demonstrate a greater level of PA in Gauteng children. Furthermore, PA levels were lower in the North-West (2.70; 95% CI: 2.67 - 2.73) compared with the Western Cape (2.88; 95% CI: 2.82 - 2.93) and KwaZulu-Natal (2.91; 95% CI: 2.85 - 2.96). The Physical Activity and Health Longitudinal (PAHL) study in the North-West province reported that 226 adolescents (16 yrs) accumulated a mean of 50.90 ± 40.30 min/day, and only 36% of the participants achieved the recommended amount of MVPA (Wushe, Moss, & Monyeki, 2014). European studies support discrepancies in PA levels amongst children residing in different countries, although the PA associations tended to focus more on socioeconomic status and gender rather than geographical area (Bürge, Tomatis, Murer, & de Bruin, 2016; Konstabel et al., 2014). PA level was estimated in 7684 European children (2-11 yrs) from eight countries including Sweden, Germany, Hungary, Italy, Cyprus, Spain, Belgium and Estonia (Konstabel et al., 2014). Two-percent Cypriot female participants met recommended amounts of 60 minutes of MVPA compared with 14.7% Swedish females. Males who met PA guidelines ranged from 9.5% to 34.1% in Italy and Belgium, respectively. Cultural differences and socioeconomic factors are most often used to explain the differences in PA prevalence between ethnic groups (Nazroo, 2003). It is interesting to note that the provinces from the present study had very different ethnic proportions. Black children were mostly from Gauteng (41%), the majority Caucasian children (49%) resided in the North-West province; and the Northern Cape province had a large proportion of other ethnic groups (29%). Similarly, ethnic proportions of the provinces from this sample show 58% Black children in Gauteng province, 85% Caucasian children in the North-West province and 30% other ethnic groups in the Northern Cape province. These ethnic proportions are supported by the overall ethnic fraction of the 80.2% Black South African population, 8.4% Caucasian South Africans and 11.3% other ethnic groups (Statistics South Africa, 2014). This has important implications when making assumptions about PA levels in a specific province. Perhaps it is more of a cultural determinant than a provincial/regional factor. In addition, provincial municipalities often reflect the values and attitudes of the culture in that province. For example, more opportunities will exist in a province that values PA and the benefits of it. In 2011, the City of Cape Town in the Western Cape province launched the first outdoor gym in

South Africa providing free gym access to the community. The project took upon a multidisciplinary approach from city officials, health care stakeholders and private sectors aiming to reduce the high levels of inactivity in the province (Pollack, 2011). Ekurhuleni Metropolitan Municipality followed this initiative a year later in Soweto, Gauteng (Sport and Recreation, 2012).

More studies have investigated Caucasian children engaging in regular PA compared with other ethnic groups (Schmitz et al., 2002; Gordon-Larson, McMurray, & Popkin, 2000). Ethnic differences in PA levels were reported in a study of 386 9-year old South African children (McVeigh, Norris, Cameron, & Pettifor, 2004). Caucasian children had greater metabolic equivalent PA scores (21.70 ± 2.90 hrs/wk) compared with Black children (9.50 ± 0.50 hrs/wk). Unlike previous studies, posthoc analyses in the present study suggested that Black children ($n = 2857$) reported significantly higher PA levels of 2% and 7.8% compared with Caucasian ($p = 0.0039$) and other ethnic groups ($p < 0.0001$), respectively. Caucasian children showed significantly higher PA levels compared with the other ethnic groups ($p < 0.0001$). Similar results were found in a cross sectional study ($n = 2071$) among 9-10 year old children in the UK (Owen et al., 2009). Specifically, Black children spent additional time engaging in vigorous PA (> 4000 cpm) and had 6% more daily activity counts when compared with their Caucasian counterparts. However, in the same study, a different pattern emerged relating to daily step counts, with the Caucasian children recording 3% more counts than the Black children. The authors concluded that objective PA instruments have a limited capacity to fully describe the diversity of PA undertaken by children. Steene-Johannessen et al. (2015) recognized that self-reported instruments have a tendency to overestimate PA levels. For example, 83% of Canadian children ($n = 55$) between 10 to 13 years old overestimated daily MVPA beyond 30 minutes, and 98% overestimated vigorous PA by 84.90 minutes per day using both a self-reported questionnaire and accelerometer (Grewal, & Simran, 2013). Taken together, measuring PA levels in general (objectively and subjectively) show some degree of error, especially in children and contribute to reported controversial findings in the proportion of children meeting PA guidelines (Reddy et al., 2012; Borges et al., 2015). Discrepancies in data have been ascribed to depend on the population studied (age, culture, and region), different analysis

procedures, and the variation in PA guidelines used by researchers (Borges et al., 2015).

The main limitation of this study is rooted in the nature of employing a questionnaire to estimate PA levels and place restrictions on the data presented by the sample. The consistency of the survey's administration is another limitation to this study in that it is unknown whether school personnel administered the questionnaire in the same way. Social desirability, recall bias, and cultural interpretations of PA contribute to the inaccuracy of reporting PA data from surveys (Steene-Johannessen et al., 2015). The true population of South African youth is likely to have lower amounts of PA than the observed levels obtained from this sample. The PAQ-C further limits the study in that it only measures general PA levels without describing specific frequency, time, or intensity (Kolwalski et al., 2004). A second limitation is the two-stage sampling method used in this study, for example, only 7 out of 9 provinces that were contacted contributed to the results. This may not reflect the diversity of the true population and therefore, results from this study should be used with caution, as the true prevalence of physical inactivity could be underestimated.

3.6 CONCLUSION

The present study generates evidence about gender, ethnic, age and provincial profiles of PA levels in South African youth. The findings suggest that South African youth engage in adequate amounts of PA. However, significant discrepancies in PA levels were found which raise important questions around population group equality in terms of access and availability to participate in PA. These results support a target approach for promoting PA levels among the high-risk groups identified in this study as females, older children, Caucasian children and other ethnic groups. The different PA levels found among provinces possibly reflect the PA priorities and cultural values of the residents and the associated municipalities. This study emphasizes the need for promoting PA equally among South African youth and serves as a sustainable objective in order to meet the health-related Sustainable Development Goals for 2030.

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CHAPTER 4: PAPER 2

Cardiac Autonomic Function and its Association with Cardiometabolic Disease Risk Factors in Black South African Children

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4.1 ABSTRACT

Purpose This study evaluated the associations between cardiac autonomic nervous system (ANS) activity and cardiometabolic disease (CMD) risk factors among black South African children. **Methods** The participants included 34 black South African children (11.85 ± 0.89 y). CMD risk factors included waist circumference (WC), hip circumference (HC), body mass index z-score (BMI z-score), blood pressure (SBP, DBP), total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), fasting glucose (FG), fasting insulin (FINS), and vessel stiffness index (SI). Heart rate variability was used to quantify cardiac ANS activity. Pearson's coefficient correlation and regression analysis were performed between CMD risk factors and HRV parameters. A p-value of ≤ 0.05 was used to indicate statistical significance. **Results** lnRMSSD, pNN50 and lnSD1 were inversely associated with FINS ($r = -0.33$, $p = 0.05$; $r = -0.36$, $p = 0.03$; $r = -0.41$, $p = 0.01$), WC ($r = -0.45$, $p = 0.01$; $r = -0.39$, $p = 0.02$; $r = -0.45$, $p = 0.01$), and HC ($r = -0.41$, $p = 0.01$; $r = -0.36$, $p = 0.03$; $r = -0.43$, $p = 0.01$). HDL was positively associated with lnRMSSD ($r = 0.37$; $p = 0.03$) and lnSD1 ($r = 0.37$; $p = 0.03$) while, LDL was negatively associated with HF ($r = -0.41$; $p = 0.01$). Regression analysis, adjusted for age and gender, identified WC as the primary predictor for parasympathetic modulation in time domain (lnRMSSD: $r^2 = 0.21$, $p = 0.01$; pNN50: $r^2 = 0.18$, $p = 0.01$) and non-linear domain (lnSD1: $r^2 = 0.21$, $p = 0.01$) HRV indices. **Conclusion** Elevated resting parasympathetic activity in children is associated with lower CMD risk factors and an elevation in the protective HDL. Efforts to eliminate ethnic-disparities in CMD ought to include interventions specially aimed at reducing these risk markers.

Keywords: cardiac autonomic nervous system, cardiometabolic disease risk factors, black children, obesity indicators, lipid profile, insulin concentrations

4.2 INTRODUCTION

The clustering of cardiometabolic disease (CMD) risk factors is becoming more prevalent in children and may be linked to ethnicity (Crowley et al. 2011). Black adolescents are reported to have higher rates of obesity, insulin-resistance and high blood pressure compared with white adolescents (Cook et al. 2008). Established and emerging CMD risk factors are associated with cardiac autonomic dysfunction and decreased parasympathetic activity (Farah et al. 2014). Cardiac autonomic function refers to the innervation of parasympathetic and sympathetic branches of the autonomic nervous system (ANS) regulating the heart (Malpas 2010). The influence of the parasympathetic and sympathetic nervous system may be measured using heart rate variability (HRV), a measure which quantifies cardiac ANS activity (Fukuba et al. 2009). Most studies examining associations between CMD risk factors and ANS activity are inconsistent and do not differentiate between different race/ethnicities (Farah et al. 2014, Xie et al. 2013, Mazurak et al. 2016).

Farah et al. (2014) found that higher body mass index (BMI) and systolic blood pressure (SBP) in Brazilian children aged sixteen-years were associated with increased sympathetic activity (LF) and decreased parasympathetic activity (RMSSD, pNN50, HF). Similarly, Paschoal, Trevizan, and Scodeler (2009) observed that increased sympathetic activity (LF, LF/HF) was positively related to waist circumference (WC) and triglycerides (TG) and negatively associated with high density lipoprotein cholesterol (HDL), but was not related to either total cholesterol (TC) or low density lipoprotein cholesterol (LDL) in Brazilian obese children (9 – 11 y). Although these studies suggest an association between CMD and sympathetic activity, the concept of the LF component to reflect sympathetic activity is flawed since it is suggested to represent both parasympathetic and sympathetic influences (Parati, Di Rienzo, and Mancia 2000). Moreover, hypertensive Chinese children demonstrated lower HRV values (SDNN, RMSSD, TP, HF) compared with their normotensive counterparts (Xie et al. 2013). In contrast to these findings, a German study found no significant difference in HRV parameters (SDNN, RMSSD, HF, LF, LF/HF) among healthy weight and obese children (9 – 17 y) (Mazurak et al. 2016).

Despite the significant volume of literature on CMD, it is unclear which risk factor accounts for the greatest variance in cardiac ANS activity and more specially, it is unclear how risk associations would present in children of black ethnicity. The inconsistent associations between individual risk factors and altered ANS activity have important implications for early ethnic-specific identification of disease risk. To address this gap, this study aimed to profile CMD risk factors among black South African children and their individual associations with ANS activity.

4.3 METHODS

Participants

Thirty-four black South African children (14 males and 20 females; 11.85 ± 0.89 y) recruited from a primary school in the province of KwaZulu-Natal participated in this cross sectional study in July 2013. The inclusion criteria included: children of black ethnicity between the ages of 10 and 13 years old (grades 4 – 7) without any known chronic disease. Approval of this study was obtained from both the institution's Research Ethics Committee (UZREC171110-030) and the KwaZulu-Natal Department of Education Institution (2/4/8/815). Written informed consent was given by the parents and assent was given by the children before participation in this study.

Procedures

All measurements were taken over five consecutive days between 9:00 AM and 12:00 PM in a quiet room at the school. The Suunto t6 monitor system was used to record 5-min interbeat intervals (IBI) in supine position (Suunto Inc; Vantaa, Finland). IBI measurements were recorded after a 5-min resting period in groups of four, due to equipment availability. Breathing rate was guided with a metronome set at 15 breaths/min (0.25 Hz). Raw IBI were manually screened for artifacts and were replaced with mean values of proceeding and preceding beats (Timonen et al. 2006). Heart rate variability indices were processed using Kubios HRV software and included time, frequency and nonlinear parameters indicative of: overall variability (SDNN, SD2), parasympathetic activity (RMSSD, pNN50, SD1, HF: 0.15 - 0.4 Hz), baroreflex activity (LF: 0.04 - 0.15 Hz) and sympathovagal balance (LF/HF) (Biosignal Analysis and Medical Imaging Group, Joensuu, Finland). Power spectral analysis was performed on both autoregressive (AR) and fast Fourier transform (FFT) spectrums.

CMD risk factors included WC, hip circumference (HC), body mass index z-score (BMI z-score), systolic and diastolic blood pressure (SBP, DBP, respectively), fasting TC, HDL, LDL, fasting glucose (FG), fasting insulin (FINS) and vessel stiffness index (SI).

WC and HC were measured in a standing position using a measuring tape. A digital scale measured body weight and was recorded to the nearest 0.1 kg. A portable stadiometer measured height and was recorded to the nearest 0.1 cm. BMI was calculated as body weight divided by height squared (kg/m^2), and BMI z-scores were based on CDC (2005) standards. Resting blood pressure was recorded in a seated position using the Welch Allyn Connex® ProBPTM 3400, a digital automated blood pressure device, after 5-min resting (Skaneateles Falls, NY 13153-0220, USA). Fasting blood samples (TC, HDL, LDL, FG, FINS) were collected by a phlebotomist after a 12-hour fasting period and analyzed following standard operation procedures (SOP) of the Lancet Pathology Laboratories (Empangeni, KwaZulu-Natal, South Africa). The PulseTrace PCA2® device (Micro Medical, Gillingham, Kent, UK) measured vessel stiffness index (SI) in supine position.

Statistical Analysis

Data are reported as arithmetic means \pm standard deviations unless otherwise stated. Normality for HRV variables were assessed by time (pre test and post-test) with the Kolmogorov-Smirnov test. Log-transformation of data was used to normalize variables with skewed distribution (lnRMSSD, lnLF/HF on FFT and AR, lnSD1). Pearson's correlation coefficient was used to measure the association between selected CVD risk factors and cardiac ANS activity parameters. Linear regression analysis, adjusted for gender and age, arranged the CMD risk factors as independent variables and cardiac ANS activity parameters as the dependent variables. A p-value of ≤ 0.05 was used to indicate statistical significance.

4.4 RESULTS

From the 34 participants, 20 were female (59%) and 14 male (41%). Participants BMI z-score (0.62 ± 1.19), SBP (105.91 ± 13.52 mmHg), and DBP (67.24 ± 8.79 mmHg) were within normal range (Zimmet et al. 2007). Blood lipid levels (TC: 3.88 ± 0.70 mmol/L; LDL: 2.13 ± 0.62 mmol/L; HDL: 1.44 ± 0.30 mmol/L), FINS (8.73 ± 7.14 uUm/L) and FG (4.70 ± 0.53 mmol/L) were within normal limits (Zimmet et al., 2007).

Mean time domain indices were recorded as SDNN 72.97 ± 28.23 ms, RMSSD 61.37 ± 33.83 ms (lnRMSSD: 3.98 ± 0.51 ms), NN50 110.65 ± 59.92 , and pNN50 $28.51 \pm 18.31\%$. lnLF/HF (0.59 ± 0.65 on FFT; 0.47 ± 0.59 on AR) revealed a high sympathovagal balance due to low HF indicative of parasympathetic withdrawal (LF: 64.43 ± 12.69 nu vs HF: 35.47 ± 12.69 nu) on FFT and on AR (LF: 60.91 ± 13.28 nu vs HF: 38.96 ± 13.19 nu). Regression coefficients (Table 1) showed that WC ($\beta = -0.01$), HC ($\beta = -0.01$), HDL ($\beta = 0.70$) and FINS ($\beta = -0.03$) explained a significant proportion of the variation in lnRMSSD ($p = 0.01$ for all).

Table 1. Regression Analysis for Parasympathetic Indicators.

Variables	lnRMSSD β (SE)	pNN50 β (SE)	HF β (SE)	lnSD1 β (SE)
BMI z-score	-0.14 (0.07)	-4.66 (2.72)	-0.02 (2.05)	-0.14 (0.07)
WC (cm)	-0.01 (0.01)*	-0.58 (0.23)*	-0.18 (0.17)	-0.01 (0.01)*
HC (cm)	-0.01 (0.01)*	-0.58 (0.25)*	-0.20 (0.19)	-0.01 (0.01)*
SBP z-score	-0.07 (0.08)	-1.92 (2.94)	-0.53 (2.13)	-0.07 (0.08)
DBP z-score	0.16 (0.12)	6.53 (4.37)	4.28 (3.17)	0.16 (0.12)
HDL (mmol/L)	0.70 (0.28)*	19.98 (10.62)	3.71 (8.06)	0.71 (0.28)*
LDL (mmol/L)	0.001 (0.15)	-0.81 (5.58)	-9.04 (3.67)*	0.001 (0.15)
TC (mmol/L)	0.07 (0.13)	1.27 (4.81)	-7.55 (3.18)*	0.07 (0.13)
FINS (uU/mL)	-0.03 (0.01)*	-1.03 (0.45)*	-0.16 (0.35)	-1.11 (0.61)
FG (mmol/L)	-0.05 (0.17)	-3.34 (6.41)	-3.37 (4.59)	-0.05 (0.17)
SI (m s⁻¹)	0.04 (0.11)	1.89 (4.27)	-1.03 (3.08)	0.04 (0.11)

Independent variables: BMI: body mass index; WC: waist circumference; HC: hip circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density protein; LDL: low density protein; TC: total cholesterol; FINS: fasting insulin; FG: fasting glucose; SI: vessel stiffness index. Dependent variables: RMSSD: root means square of successive differences; pNN50: percentage of R-R intervals greater than 50 ms; HF: high frequency band on AR spectrum; SD1: standard deviation 1 on Poincare plot. * $p < 0.05$.

Overall Variability

SDNN and SD2 indices were reflective of overall variability. SDNN ($r = 0.37$; $p = 0.03$) and SD2 ($r = 0.37$; $p = 0.03$) were positively associated with HDL. Following regression analysis, adjusted for gender and age, both SDNN ($r^2 = 0.14$; $p = 0.04$) and SD2 ($r^2 = 0.13$; $p = 0.04$) remained associated with HDL.

Parasympathetic Activity

Indices of parasympathetic activity included RMSSD, pNN50, HF and SD1. lnRMSSD was negatively associated with BMI z-score ($r = -0.34$; $p = 0.04$), WC ($r = -0.45$; $p = 0.01$), HC ($r = -0.43$; $p = 0.01$) and FINS ($r = -0.41$; $p = 0.01$) and positively associated with HDL ($r = 0.42$; $p = 0.01$). Regression analysis revealed significant independent associations for lnRMSSD with WC ($r^2 = 0.21$; $p = 0.01$), HC ($r^2 = 0.19$; $p = 0.01$), FINS ($r^2 = 0.17$; $p = 0.02$) and HDL ($r^2 = 0.17$; $p = 0.01$).

pNN50 showed associations with WC ($r = -0.39$; $p = 0.02$), HC ($r = -0.36$; $p = 0.03$) and FINS ($r = -0.36$, $p = 0.03$). Independent associations were also noted for pNN50 with WC ($r^2 = 0.18$; $p = 0.01$), HC ($r^2 = 0.16$; $p = 0.02$) and FINS ($r^2 = 0.15$; $p = 0.03$).

HF was significantly associated with LDL ($r = -0.41$; $p = 0.01$) on the AR spectrum. Following regression analysis, HF demonstrated an independent association with LDL ($r^2 = 0.17$; $p = 0.01$) and a dependent association with TC ($r^2 = 0.16$; $p = 0.02$) on the AR spectrum.

lnSD1 was found to be significantly associated with BMI z-score ($r = -0.34$; $p = 0.04$), WC ($r = -0.45$; $p = 0.01$), HC ($r = -0.43$; $p = 0.01$), FINS ($r = -0.41$; $p = 0.01$) and HDL ($r = 0.42$; $p = 0.01$). lnSD1 was independently associated with WC ($r^2 = 0.21$; $p = 0.01$), HC ($r^2 = 0.19$; $p = 0.01$) and HDL ($r^2 = 0.17$; $p = 0.01$).

Baroreflex Activity

LF is considered an indicator of baroreflex activity modulated by both the parasympathetic and sympathetic nervous system. On the AR spectrum, LF showed a significant association with LDL ($r = 0.41$; $p = 0.02$) and remained independently associated ($r^2 = 0.17$; $p = 0.02$). TC ($r^2 = 0.16$; $p = 0.02$) revealed a significant

association with LF following regression analysis despite not being significantly associated with Pearson's correlation, indicating a dependent association.

Sympathovagal Balance

lnLF/HF, an indicator of sympathovagal balance, had significant associations with LDL ($r = 0.40$; $p = 0.01$) and TC ($r = 0.39$; $p = 0.02$) on the AR spectrum. LDL ($r^2 = 0.16$; $p = 0.02$) and TC ($r^2 = 0.15$; $p = 0.02$) remained significant following regression analysis on the AR spectrum.

An additional dependent association with WC ($r^2 = 0.17$; $p = 0.02$) on the FFT spectrum was noted.

4.5 DISCUSSION

This study is the first to report on the individual associations between CMD risk factors and ANS activity among black South African children. The primary findings of this study indicate that: overall variability (SDNN, SD2) is independently associated with HDL; parasympathetic activity (lnRMSSD, pNN50, HF, lnSD1) is independently associated with WC, HC, HDL, LDL and FINS; baroreflex activity (LF) is independently associated with LDL; and higher lnLF/HF ratio due to lower HF is independently associated with higher levels of TC and LDL.

Chinese and Brazilian studies have reported associations between parasympathetic activity and CMD risk factors in children (Zhou et al. 2012, Farah et al. 2013). A cross sectional study of 180 Chinese children (9 – 11 y) found a decrease in parasympathetic activity (RMSSD, HF) with increasing BMI and WC (Zhou et al. 2012). Similarly, Farah et al. (2013) reported reduced parasympathetic activity (RMSSD, pNN50) in 74 Brazilian obese normotensive adolescents (13 – 18 y) that had higher WC (RMSSD: $r^2 = 0.15$, $p = 0.039$; pNN50: $r^2 = 0.16$, $p = 0.033$), however, in contrast to Zhou et al. (2012), BMI was not significantly associated with any HRV indices (Farah et al. 2013). The authors proposed that parasympathetic modulation is related to central obesity rather than general obesity in obese normotensive adolescents. In 2014, Farah et al. revealed the same correlation between WC and pNN50 but opposing results for

BMI that negatively correlated with HF among 1152 Brazilian adolescent boys (16 y). The results from the latter study indicated an additional association between parasympathetic activity (RMSSD, pNN50, HF) and blood pressure (SBP, DBP). Elevated SBP also correlated with lower parasympathetic activity (RMSSD, HF) in 101 Chinese children (10 y) (Xie et al. 2013). This is in contrast with the present study's findings that had observed no association between blood pressure and any HRV parameter. The conflicting results reported for blood pressure may be explained by the different age groups examined by Farah et al. (2014) who reported on adolescents (16 y) and Xie et al. (2013) findings were based on hypertensive children (9 – 11 y). Tanaka et al. (2000) support this notion with results demonstrating significant correlation between resting arterial pressure and sympathovagal balance (LF/HF) among 56 adolescents (13 – 16 y), but not among 71 preadolescents (6 – 12 y). The authors proposed that blood pressure levels may only be associated with cardiac ANS activity during and after puberty and not during preadolescence. This is consistent with the present study's findings that revealed no association between blood pressure and LF suggested to reflect baroreflex activity.

Finally, regression analysis, adjusted for age and gender, from the current study's findings identified WC as the primary predictor for parasympathetic modulation in time domain (lnRMSSD: $r^2 = 0.21$, $p = 0.01$; pNN50: $r^2 = 0.18$, $p = 0.01$) and non-linear domain (lnSD1: $r^2 = 0.21$, $p = 0.01$) HRV indices, while LDL revealed to be the major determinant in frequency domain (HF: $r^2 = 0.17$, $p = 0.01$). Furthermore, regression coefficients indicated that a 1 mmol/L increment in HDL is associated with an increase of 0.70 ms lnRMSSD and 0.71 ms lnSD1.

4.6 CONCLUSION

The findings from this study suggest that obesity indicators (WC, HC), lipid profile (LDL, HDL) and insulin concentrations relate to parasympathetic activity in black South African children. This may have important implications for the prognosis of CMD in this population. Efforts to eliminate ethnic-disparities in CMD ought to include interventions specially aimed at reducing these risk markers. The lack of a control group and another

racial group may be a limitation of the current study. This study is the first to provide normative values for HRV in black South African children. Further pediatric studies are required in order to differentiate HRV indices among ethnicity, gender and their associations with the more commonly reported CMD risk factors.

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CHAPTER 5: PAPER 3

Modification of Cardiometabolic Disease Risk Factors in Overweight Children: An Exploratory Study of Different Exercise Doses

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5.1 ABSTRACT

Purpose The purpose of this study was to assess the effects of two different exercise doses on cardiometabolic risk factors in overweight children. **Methods** Participants were randomly assigned to either moderate-intensity high-frequency exercise or vigorous-intensity low-frequency exercise for a total duration of 6 weeks. The moderate-intensity high-frequency group (n = 5) participated in 30 sessions, which were set at 40% – 60% of heart rate reserve. The vigorous-intensity low-frequency group (n = 7) participated in 18 sessions, which were set at 60% – 80% heart rate reserve. **Results** The results showed that fasting glucose level (- 6.79%, $p < 0.13$) responded better to moderate-intensity high-frequency exercise whereas vigorous-intensity low-frequency exercise induced greater improvements in systolic blood pressure (- 5.98%, $p < 0.23$) with a mean change of -6.4 mmHg. **Conclusion** This study showed that two different exercise doses improved selected cardiometabolic variables in overweight children. Hence, this study provides exercise recommendations for achieving specific cardiometabolic health benefits in overweight children.

Keywords: cardiometabolic disease risk factors, obesity, overweight children

5.2 INTRODUCTION

The percentage of overweight primary school children in South Africa increased from 1.2% in 1994 to 13% in 2004 (Armstrong et al., 2011). Although morbidity from obesity-related disorders (e.g. cancer, congestive heart failure, pulmonary embolism, chronic renal failure, and depression) generally manifests during adult years, the pathological processes begin during pediatric years (Guillaume et al., 1997; Shalitin et al., 2009; Gutin & Owens, 2011). The NAHSIT-ESC (Nutrition and Health Survey in Taiwan Elementary School Children) survey reported that obese children have higher blood pressure, triglyceride levels, low-density lipoprotein cholesterol, uric acid, and serum glutamic pyruvic transaminase levels when compared with normal weight children (Chu, 2005; Chu & Pan, 2007). The prevalence of children leading sedentary lifestyles has increased over the years, and a variety of environmental factors have contributed to this problem. Two key environmental factors that have fueled the obesity epidemic are diets rich in fat and processed carbohydrates as well as physical inactivity (Shalitin et al., 2009). Regular physical activity (PA) lowers the prevalence of cardiometabolic disease risk factors (Sattelmair et al., 2011). The progression and associated complications of the disease is best modified during early years (Barbeau et al., 2007). A range of substantial health benefits is associated with accumulating 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity PA per week (ACSM, 2010). Classification of the required amount of PA is possible when considering the metabolic equivalent of activities, though restrictions exist when assigning energy costs in children (Spadano et al., 2003; Warburton, Nicol, & Bredin, 2006; Bushman, 2012). Several studies question the effectiveness of the recommended PA guidelines for children in preventing cardiovascular disease risks (Andersen et al., 2006; Gutin & Owens, 2011). An observational study suggests that 90 minutes of moderate-intensity PA per day is necessary to prevent insulin resistance in children (Andersen et al., 2006). In contrast, meta-analysis revealed that vigorous-intensity PA is more effective in modulating biomarkers and is associated with greater improvements in fitness and fat percentages in youth compared with moderate-intensity PA (Gutin & Owens, 2011).

The global obesity epidemic will likely result in the prevalence of cardiometabolic disease risk factors manifesting at younger and younger ages, yet little evidence is available on the particular exercise prescription for reducing cardiometabolic disease risk factors in children. Therefore, the current study sought to investigate the effect of 2 different exercise doses on cardiometabolic disease risk factors in overweight children.

5.3 METHODS

Participants

A convenience sample of twelve (nine male, three female) 11-13-year-old children were recruited from the Zululand area in South Africa. Nine participants were Caucasian, and 3 were African. Participants were screened prior to the inclusion in the study to ensure that the requirements of being classified as overweight were met (Heber, 2002). Participants taking chronic medications that are known to affect heart rate/pulmonary function were excluded. The study was approved by the Ethics Committee of the Faculty of Science & Agriculture at the University of Zululand, South Africa. Signed informed assent and consent forms were obtained from the participants and parents or guardians of the participants.

Instruments and Measurements

Data collection took place over three consecutive days. Post-measurements were taken within a week after the participants completed the exercise programs.

Target Heart Rate

Target heart rate was measured continuously using a polar heart rate monitor during the exercise programs. This ensured the set target heart rate ranges for the respective exercise groups. More specifically, the target heart rate ranges were calculated using the Karvonen method with heart rate reserve (HRR), accounting for individual resting heart rate. Resting heart rate was measured in a private classroom after sitting quietly for 5 minutes. The target heart rate range of the moderate-intensity high-frequency (MIHF) group was calculated at 40% – 60% of HRR, and that of the

vigorous-intensity low-frequency (VILF) group was set at an intensity range of 60% – 80%. Alarms were set on polar watches to denote deviancy of intensity.

Resting Blood Pressure

Blood pressure was assessed manually using a Nantong Honsun (Co. Ltd, China) sphygmomanometer and stethoscope. Measurements were recorded in millimeters of mercury (mmHg). Blood pressure was assessed in a seated position after participants rested quietly for 5 minutes.

Fasting Glucose & Total Cholesterol

Fasting blood glucose and total cholesterol levels were measured using an Accu-chek® Performa (Roche Diagnostics, Germany) system early in the morning after fasting for >10 hours (ACSM, 2010). Samples were obtained via finger prick.

Anthropometric Measurements

Stature and body mass of the participants were measured using a stadiometer and a digital metric scale to the nearest 0.1 cm and 0.1 kg respectively. BMI percentile was calculated for the participant inclusion criteria. A measuring tape was used to obtain waist and hip circumferences to the nearest 0.1 cm (ACSM, 2010). Participants were bare footed and dressed in PE attire (lightweight shorts and collar shirts).

Cardiorespiratory fitness

Participants completed the 20-meter shuttle run test to obtain indirect $\text{VO}_{2\text{max}}$ values (Leger et al., 1988). Participants were encouraged and guided through the test up to the point where they could not complete the specific level of the test. The latter was recorded on individual data sheets immediately after the level failure. The formula for estimating VO_2 peak was calculated as $\text{VO}_2 \text{ peak} = 31.025 + 3.238 \text{ Speed (km/h)} - 3.248 \text{ Age (years)} + 0.1536 \text{ Speed} \times \text{Age}$ (Leger et al., 1988).

Exercise Program Protocols

The moderate-intensity high-frequency (MIHF) exercise was set at 40% - 60% of HRR and consisted of 30 sessions (5 days/wk). The vigorous-intensity low-frequency (VILF) exercise entailed 18 sessions (3 days/wk) set at 60% - 80% of HRR. Both 6-week exercise protocols were a combination of cardiorespiratory and body weight resistance activities that lasted 40 minutes in total. Each session was divided into warm-up, cool-down and work-out periods. All sessions were conducted on the sports field at the school after school hours. Sessions were moved to the school hall in the event of bad weather. Each participant was fitted with a polar heart rate monitor before the start of the exercise session. Table 1 outlines the specific activities that were included within the exercise protocols (McKenzie et al., 2000). Exercise activities and volumes (work: rest, repetitions and duration) that are shown in the table are estimated and were adjusted according to target heart rates and motivation/interest of participants.

Table 1. Overview of 6-Week Activities

WEEK	MIHF GROUP (40% - 60% HRR)	VILF GROUP (60% - 80% HRR)
1	Climbing steps (5 × 2; 30 s rest) Gallop 10m (5 × 1; 15 s rest) Hula hoop (1 min × 3; 30 s rest) Lunges (5 with each leg × 2; 30 s rest) Crunches (20 × 3; 30 s rest) Leg lifts (20 with each leg × 2; 30 s rest) One hundreds (100 counts × 2; 30 s rest) Ladies push-ups (8 × 2; 30 s rest) Pelvic lifts (20 × 2; 15 s rest) Skipping rope (20 s × 3; 30 s rest)	Jumping jacks (15 jumps × 5; 15 s rest) Hop on one leg between rugby goal posts (One leg there, other leg back × 3; 15 s rest) Sprint 10m (5 × 1; 10 s rest) Jump 10m (5 × 1; 10 s rest) Squats (10 × 4; 15 s rest) Crunches (20 × 3; 30 s rest) Cross over crunch (10 × 2; 30 s rest) One hundreds (100 counts × 2; 30 s rest) Leg lifts on a side (20 × 2; 30 s rest) Ladies push-ups (8 × 2; 30 s rest) Plank (30 s × 2; 30 s rest) Skipping rope (30 s × 5; 30 s rest)
2	BOOTCAMP WEEK (15 reps 3 sets)	BOOTCAMP WEEK (20 reps 4 sets)

	<i>Rest 2 min between sets</i> Squats Fast feet Twist bend knee sit up Burpies Arm lifts High knees Side bends In and out hops Floor swimming Kick buttock Walking lunges Scissor jumps	<i>Rest 1 min between sets</i> Squats Fast feet Twist bend knee sit up Burpies Arm lifts High knees Side bends In and out hops Floor swimming Kick buttock Walking lunges Scissor jumps
3	Jumping Jacks (15 × 3; 30 s rest) 1-Leg jumps on a spot (15 × 1; 15 s rest) Hula hopscotch (5 min; 30 s rest) Squats (8 × 2; 30 s rest) Heal taps (20 × 2; 30 s rest) Side plank (20 s × 2; 30 s rest) Zigzag running (2 min; 30 s rest) Bridge hold (30 s × 4; 30 s rest) Tricep dips on chair (8 × 2; 30 s rest) Crunches 45° arms (20 × 2; 30 s rest)	Jumping Jacks (15 × 5; 15 s rest) 1-Leg jumps on a spot (15 × 2; 10 s rest) Hula hopscotch (2 min × 3; 10 s rest) Squats (8 × 2; 15 s rest) Heal taps (20 × 3; 10 s rest) Side plank (20 s × 2; 10 s rest) Zigzag running (2 min × 3; 10 s rest) Bridge hold (30 s × 4; 10 s rest) Tricep dips on chair (8 × 2; 15 s rest) Crunches 45° arms (20 × 2; 15 s rest)
4	Agility T-run (4 sets; 45 s rest) 10m Ladder run for (5 min) 10m Hula hoop hurdles (5 min) Builders and bulldozers (7 min) Freeze and go (4 sets) Climbing stairs (3 min; 1 min rest)	Agility T-run (6 sets; 30 s rest) 10m Ladder run for (7 min) 10m Hula hoop hurdles (7 min) Builders and bulldozers (10 min) Freeze and go (6 sets) Climbing stairs (5 min; 1 min rest)
5	Toss bean bag in air and catch it (3 min)	Toss bean bag in air and catch it (5 min)

	Crust & Crumbles (<i>7 min</i>) Frog jumps, Grandpa walk, Crab sidewalks (<i>7 min</i>) Quiz (Star jumps, Burpies) (<i>7 min</i>) High knees Kick bum Jog Grapevine Fast feet sideways Sprint Run backwards	Crust & Crumbles (<i>10 min</i>) Frog jumps, Grandpa walk, Crab sidewalks (<i>8 min</i>) Quiz (Star jumps, Burpies) (<i>10 min</i>) High knees Kick bum Jog Grapevine Fast feet sideways Sprint Run backwards
6	Circuit training (<i>10 min</i>) Resistance bands-leg lifts, ball-lift from ground to sky SLOWLY, weights-bicep curls, mat-crunches Moving around the track 7 m × 7 m (<i>5 min</i>) Jogging Aerobic bowling Star jumps, scissor jump (<i>8 min</i>) Jump back and forth over rope (<i>10 jumps each</i>) Ocean wave, snake in the grass Four lines (<i>5 min</i>) 1, 2, 3, 4	Circuit training (<i>10 min</i>) Resistance bands-leg lifts, ball-lift from ground to sky FAST, weights-bicep curls, mat-crunches Moving around the track 10 m × 10 m (<i>5 min</i>) Sprinting Aerobic bowling Star jumps, burpies (<i>8 min</i>) Jump back and forth over rope (<i>20 jumps each</i>) Ocean wave, snake in the grass Four lines (<i>10 min</i>) 1, 2, 3, 4

Data Analysis

Descriptive data are expressed as means, standard deviations (SD) and percentage change. Pearson Correlation Coefficients were used to assess associations between variables. The Mann-Whitney U test was utilized to compare measurements between the two exercise groups and the Wilcoxon signed-rank test was calculated to

determine pre and post-intervention measures within each group. Significance was set at $p < 0.05$ using GraphPad Prism® (GraphPad Software. Inc., CA, USA).

5.4 RESULTS

Five ($n = 5$) participants completed 30 sessions of MIHF, and seven ($n = 7$) participants completed 18 sessions of VILF. The main findings of this study showed that two different exercise doses elicited specific cardiometabolic benefits in overweight children. Fasting glucose level (-6.79% , $p < 0.13$) responded better to MIHF, whereas VILF provided greater improvements in systolic blood pressure (-5.98% , $p < 0.23$). Mean values and percentage change are presented in table 2.

Table 2. Pre-post changes in CMD risk factors in participants

Variables	MIHF Group ($n = 5$)				VILF Group ($n = 7$)			
	Pre test Mean \pm SD	Post test Mean \pm SD	% Change	p	Pre test Mean \pm SD	Post test Mean \pm SD	% Change	p
BM (kg)	76.1 \pm 12.93	75.6 \pm 13.85	-0.66%	0.44	76.11 \pm 19.01	77.31 \pm 20.43	1.58%	0.23
BMI (kg/m^2)	31.05 \pm 5.05	30.85 \pm 5.37	-0.64%	0.44	29.9 \pm 4.97	30.34 \pm 5.48	1.47%	0.22
WC (cm)	91.60 \pm 10.01	84.2 \pm 10.03	-8.08%	0.06	91.14 \pm 9.62	86.14 \pm 12.85	-5.49%	0.03*
HC (cm)	107 \pm 7.97	103.4 \pm 7.64	-3.36%	0.13	105.9 \pm 12.5	101.4 \pm 12.53	-4.25%	0.09
SBP (mmHg)	110.60 \pm 8.53	108 \pm 9.27	-2.35%	0.63	107.1 \pm 10.82	100.7 \pm 10.56	-5.98%	0.23
DBP (mmHg)	72 \pm 10.30	68.8 \pm 10.35	-4.44%	0.63	68 \pm 7.30	61.71 \pm 10.8	-9.25%	0.23
FBG (mmol/L)	4.42 \pm 0.28	4.12 \pm 0.30	-6.79%	0.13	4.67 \pm 0.67	4.36 \pm 0.44	-6.64%	0.06
TC (mmol/L)	4.25 \pm 0.41	4.52 \pm 0.69	6.35%	0.31	4.42 \pm 0.60	4.59 \pm 0.59	3.85%	0.47
VO _{2max}	39.17 \pm	40.68 \pm	3.71%	0.25	41.16 \pm	41.89 \pm 3.95	1.74%	0.62

(ml/kg/min)	2.58	3.48			3.65			
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BM: body mass; BMI: body mass index; WC: waist circumference; HC: hip circumference SBP: systolic blood pressure; DBP: diastolic blood pressure; FBC: fasting blood glucose; TC: total cholesterol; VO_{2max} : maximal volume of oxygen. *significant reduction set at $p < 0.05$.

5.5 DISCUSSION

The purpose of this study was to determine if two different exercise doses would impact differently on cardiometabolic disease risk factors in overweight children.

Pearson correlations shown in table 3 show that participants with high body mass and body mass index presented lower fitness levels, higher-waist circumference, -blood pressure, -total cholesterol and -fasting blood glucose. CRF is known to increase mortality in adults, though there is a the lack of research in children. CRF is a variable that can be easily modified with physical activity interventions.

Table 3. Pearson Coefficient Correlation between Body Mass (kg) and Body Mass Index (kg/m²) at baseline for n = 12 participants

	VO_{2max} (ml/kg/min)	SBP (mmHg)	DBP (mmHg)	FBG (mmol/L)	TC (mmol)	WC (cm)
BM (kg)	-0.24	0.2	0.36	0.13	0.72	0.94
BMI (kg/m²)	-0.48	0.34	0.23	-0.08	0.5	0.86

BM: body mass; BMI: body mass index; WC: waist circumference; DBP: diastolic blood pressure; SBP: systolic blood pressure; TC: total cholesterol; FBC: fasting blood glucose; VO_{2max} : maximal volume of oxygen.

Waist circumference and cardiorespiratory fitness were improved by -8.08% and 3.78%, respectively, in the MIHF group. These improvements were associated with marginal reduction in body mass (-0.5 kg). Interestingly, the VILF group showed a slight increase in body mass (1.2 kg), yet still showed improvements of -5.49% and 1.76% for the same variables. Research has indicated that girls (>37 ml/kg/min) and boys (>42.1 ml/kg/min) with higher cardiorespiratory fitness levels were 3.09 and 2.42 times,

respectively, more likely to have a lower metabolic disease risk profile (Ruiz et al., 2007).

Maximal volume of oxygen, an indirect measurement of cardiorespiratory fitness, showed an inverse correlation with body mass ($r = -0.27$) and body mass index ($r = -0.48$). A cross sectional study has established significant inverse associations with cardiorespiratory fitness and the clustering of metabolic risk factors in children (Machado-Rodrigues et al., 2014). Several studies have investigated the independent values of cardiorespiratory fitness, body mass index and waist circumferences for predicting cardiometabolic risk in children (Buchan et al., 2015; Burgos et al., 2015). The body mass index and waist circumference changes were most evident due to the clustering of cardiometabolic risk with body mass index, which is described as the main predictor in Brazilian children (Burgos et al., 2015). This is consistent with strong to very strong associations found with body mass in the current study for total cholesterol ($r = 0.72$) and waist circumference ($r = 0.94$). Weaker associations were reported with SBP ($r = 0.2$), DBP ($r = 0.36$) and FBG ($r = 0.13$). SBP ($r = 0.34$) showed stronger association with body mass index.

While most variables showed a trend towards improvement, the increases in total cholesterol and body mass were observed in the groups. Similar increases in triglycerides in overweight/obese children were found after an 8-week exercise program (Patel et al., 2015). The latter study concluded that the growth-related increased lipid mobilization during puberty was a critical contributing factor for this finding. It appears that serum cholesterol levels are more likely to change with a combination of diet and exercise interventions in obese children (Christiansen et al., 2010). A 6-week combined intervention program improved total cholesterol with a mean reduction of -0.8 mmol/L in obese girls and -0.88 mmol/L in obese boys (Luo et al., 2013).

Both exercise groups demonstrated modest improvements of blood pressure. This change seems to be a more pronounced in the VILF group. The mean systolic blood pressure change for participants in this group was -6.4 mmHg. In the same group, mean diastolic blood pressure was reduced from 68 mmHg to 61.71 mmHg. A systematic analysis of nineteen studies that evaluated the effect of childhood obesity prevention programs (physical activity, diet and their combinations) observed an

average reduction of -1.64 mmHg in SBP and -1.44 mmHg in DBP (Cai et al., 2014). The MIHF group achieved similar reductions of -2.6mm Hg in SBP and -3.2 mmHg in DBP. Clinical studies suggest that even a small reduction in blood pressure has beneficial effects on reducing cardiovascular disease morbidity and mortality (Kelley & Kelley, 2000). A decrease in systolic blood pressure by 5 mmHg, reduces deaths from stroke by 14% (Whelton, He, & Appel, 2002).

Research suggests that large amounts of exercise are not required for improving metabolic profiles when lower volumes can achieve similar reductions and are more convenient for overweight children (Chen, Roberts & Barnard, 2006). The modest changes observed in cardiometabolic risk factors in this study are supported by meta-analyses that investigated the effects of exercise in children (Cai et al., 2014; Shaibi et al., 2015). In the current study, it was interesting to note that cardiorespiratory fitness induced improvements in SBP, DBP, WC and FBG without significant weight loss.

Research acknowledges cardioprotective benefits of exercise interventions but points out that slight modifications in traditional risk factors alone cannot explain this benefit (Green et al., 2011). Subclinical changes induced by exercise provide further explanation for reduced disease risk with marginal clinical improvements. The focus on clinical markers as the primary inclusion criteria for exercise intervention studies can underestimate subclinical events of atherosclerosis that occurs in children (Barlow, 2007; Shaibi et al., 2015). More attention should be given to screening and monitoring subclinical markers during exercise interventions.

The absence of monitoring average target heart rates and energy expenditure per session are major limitations that will be useful to address in future studies. Furthermore, the small sample size, indirect measurement of cardiorespiratory fitness and the lack of dietary control limit the validity of assumptions that are made in this study. Lastly, it is difficult to say which exercise variable (frequency and intensity) induced the most benefits.

5.6 CONCLUSION

Despite the limitations, this study suggests that MIHF and VILF exercise protocols may impart favorable changes on selected cardiometabolic disease risk factors. The lack of statistical significance underlies percentage changes that taken together may confer clinical benefits for children. This needs to be confirmed using larger sample sizes and a non-exercising control group. The latter may see us advocate for programs that include a combination of exercise doses to produce the most meaningful outcomes.

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CHAPTER 6: PAPER 4

Do Short-term Exercise Interventions Improve Cardiometabolic Risk Factors in Children?

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6.1 ABSTRACT

Purpose This study aimed to explore the impact of short-term exercise of varying intensity on traditional cardiometabolic disease (CMD) risk factors. **Methods** One hundred-and-nine children (11.1 ± 0.8 y) were conveniently assigned to 5-weeks of either: moderate intensity continuous training (MICT; $n = 29$) set at 65% – 70% of maximum heart rate (MHR); high intensity interval training (HIIT; $n = 29$; $> 80\%$ MHR); combined training (HIIT + MICT; $n = 27$); or no training (CT; $n = 24$). A two-way analysis of variance (group x time) was used to evaluate the effects of training on all CMD risk factors. Effect sizes (ES) were calculated to assess the magnitude of difference. **Results** MICT, HIIT and HIIT + MICT was associated with significantly improved resting heart rate (ES = -0.4; ES = -1.1; ES = -1.1; $p < 0.0001$), fasting glucose (ES = -0.6; ES = -0.9; ES = -0.1; $p = 0.0004$), peak oxygen consumption (ES = 0.5; ES = 0.9; ES = 0.5; $p < 0.0001$) and c-reactive protein (ES = -0.2; ES = -1.0; ES = -0.5; $p = 0.0016$), respectively. HIIT + MICT was significantly associated with reduced waist circumference (-5.4%; $p < 0.0001$) and waist-to-hip ratio (-2.5%; $p < 0.0002$) compared with the MICT (7.0%; 6.3%) and HIIT (-0.5%; -1.3%) groups, respectively. **Conclusion** The findings from this study indicate that short-term HIIT and MICT interventions are both useful for improving cardiometabolic health in children. HIIT + MICT may provide superior reductions in central obesity indicators.

Keywords: exercise intensity, high-intensity interval training, moderate-intensity continuous training

6.2 INTRODUCTION

Low physical activity (PA) levels and sedentary lifestyles have been identified as contributory factors for CMD (Freedman, Mei, Srinivasan, Berenson, & Dietz, 2007). Consequently, it has been proposed that sufficient PA may improve cardiometabolic health in children (WHO, 2010). Pediatric PA guidelines (6 – 17 y) issued by the US Department of Health and Human Services (USDHHS) recommend 60 minutes of daily moderate-to-vigorous PA (USDHHS, 2008). However, it has been proposed that the current recommended amounts of PA are insufficient for modifying composite-cardiovascular risk score in children and are limited to improving body composition and cardiorespiratory fitness (Füssenich et al., 2016). This has led to research investigating the impact of different exercise intensities on cardiometabolic health in children. For example, Tan et al. (2017) demonstrated the effectiveness of a 10-week moderate intensity exercise program (50% HRR) on significantly decreasing systolic blood pressure (SBP), body mass index (BMI), waist circumference (WC), body fat percentage, and fat mass. Weston et al. (2016) achieved significant improvements for WC and triglycerides after a 10-week high intensity exercise program ($\geq 90\%$ VO_2peak). Buchan et al. (2011) evaluated the impact of a 7-week traditional moderate intensity continuous program versus a high intensity interval training (HIIT) program in adolescents. The findings revealed distinct cardiometabolic benefits induced by the two different exercise intensities. Likewise, Racil et al. (2016) randomly assigned 47 obese adolescents to either a 12-week moderate intensity interval training (MIIT) program or a HIIT program. Both groups demonstrated significant improvement in CMD risk factors from baseline to post intervention. Few differences between the groups were reported, however those observed tended to favor the HIIT group.

This study aimed to explore the impact of a short-term exercise intervention of varying intensities on traditional CMD risk factors.

6.3 METHODS

The final sample included one hundred-and-nine ($n = 67$ females; $n = 42$ males) participants between the ages of 10 and 13 years old (11.1 ± 0.8 y) with no known chronic disease. This study was approved by the institution's Research Ethics Committee (UZREC171110-030). Permission to conduct this study was granted by the KwaZulu-Natal Department of Education Institution (2/4/8/815). Written informed consent and assent were obtained by parents and children, respectively, prior to participation of this study.

Fasting glucose (FG), fasting insulin (FINS) levels and C-reactive protein (CRP) were collected after an overnight fast and analyzed by Lancet Pathology Laboratories (Empangeni, KwaZulu-Natal, South Africa). Blood analysis followed the standard operation procedures of this accredited pathology laboratory. WC and hip circumference were measured to the nearest 0.1 cm using a measuring tape. Height and weight were measured with a stadiometer and a digital metric scale to the nearest 0.1 cm and 0.1 kg, respectively. SBP and diastolic blood pressure (DBP) were measured twice (recording the average value in mmHg and a third measure if differed by > 5 mmHg) in a seated position after 5 min of rest, with the Welch Allyn Connex® ProBPTM 3400 (Skaneateles Falls, NY 13153-0220, USA). This device meets the requirements of the Association for the Advancement of Medical Instrumentation (AAMI) standard (Alpert, 2007).

Vessel stiffness index (SI), an indicator of large artery stiffness, was derived from digital volume pulse using the PulseTrace PCA2® photoplethysmographic device (Micro Medical, Gillingham, Kent, UK). This device has been used in previous pediatric studies and has been validated by comparing it with carotid-femoral pulse wave velocity, the gold standard for measuring arterial stiffness (Veijalainen et al., 2013; Veijalainen, Tompuri, Lakka, Laitinen, & Lakka, 2011). The average of two SI measurements was calculated and expressed as meters per second. Participants were tested while lying supine. Peak oxygen consumption (VO_{2peak}) was estimated using the 20-meter shuttle run test (Léger et al., 1988). Léger and Lambert's (1982) equation [$VO_{2peak} = 31.025 +$

$(3.238 \times \text{velocity}) - (3.248 \times \text{age}) + (0.1536 \times \text{age} \times \text{velocity})]$ was used to obtain indirect $\text{VO}_{2\text{peak}}$ values.

Participants were conveniently assigned to either the moderate intensity continuous training (MICT) intervention, HIIT intervention, combination of MICT and HIIT interventions on alternating weeks (HIIT + MICT), or the control (CT) group (Table 1). The CT group was not exposed to any intervention.

Table 1. Exercise Interventions

Variable	MICT (n = 29)	HIIT (n = 29)	HIIT + MICT (n = 27)
Protocol	33 min Continuous Brisk Walking	10 x (1 min; 75 s active rest) Sprinting	10 x (1 min; 75 s active rest) Sprinting; 33 min Continuous Brisk Walking
Frequency (p/w)	3 Sessions per week	3 Sessions per week	3 Sessions per week
Intensity (MHR)	65% – 70% MHR	>80% MHR	65% – 70% MHR; > 80% MHR
Duration (min)	33 min per Session	23 min per Session	33 min per Session; 23 min per Session
Total Sessions	15 Session	15 Session	15 Session (9 HIIT; 6 MICT)

HIIT: high-intensity interval training; MICT: moderate-intensity interval training; MHR: maximal heart rate.

The participants in the MICT group performed 33 minutes of continuous brisk walking at an intensity level set at 65% – 70% of their predicted maximum heart rate (MHR). The HIIT group completed 10 intervals of 1 minute sprinting set at > 80% of their predicted MHR. Each interval was followed by 75 seconds of active recovery that involved walking backwards at an intensity of < 70% of their predicted MHR. The total duration of each HIIT session amounted to 23 minutes. The HIIT + MICT group entailed both MICT and HIIT interventions on alternating weeks. This resulted in three non-consecutive weeks of HIIT (9 sessions in total) and two non-consecutive weeks of MICT (6 sessions in total).

The fifteen training sessions of HIIT, MICT and HIIT + MICT, performed three times weekly over 5-weeks, were supervised by trained Biokinetics students and

occurred during school hours on the school's sports ground. All sessions included a 5-minute warm up and cool down consisting of jogging at a low intensity followed by static stretching. Exercise intensities were controlled and monitored using the Suunto M1 heart rate monitor (Suunto Oy, Finland).

Data are presented as arithmetic means \pm standard deviations unless otherwise stated. A two-way analysis of variance with repeated measures was used to evaluate group \times time interactions and effects of group or time on all variables ($p < 0.05/4 = 0.0125$). Effect sizes (ES) were calculated and the values were interpreted as follows: > 0.8 is a large, 0.5 is a medium and < 0.2 is a small effect (Cohen, 1988).

6.4 RESULTS

Participants ($n = 109$) included 67 girls (61%) and 42 boys (39%). Descriptive statistics are presented in Table 2. Following 5-weeks of training, the HIIT group recorded a mean training heart rate of 169.9 ± 3.9 bpm compared with 140.4 ± 4.3 bpm and 157.4 ± 14.7 bpm in the MICT and HIIT + MICT groups, respectively. There was no significant difference in the estimated energy expenditure between the three exercise interventions ($p > 0.61$). This may imply an isocaloric outcome over 15 sessions of HIIT (156.0 ± 6.6 kcal), MICT (154.3 ± 8.7 kcal), and HIIT + MICT (154.2 ± 5.0 kcal). Furthermore, total exercise time over 5-weeks was 345 min (HIIT), 495 min (MICT), and 405 min (HIIT + MICT).

Table 2. Exercise Intervention Effects on CMD Risk Factors

Variable	MICT (n = 29) M \pm SD		HIIT (n = 29) M \pm SD		HIIT + MICT (n = 27) M \pm SD		Control (n = 24) M \pm SD	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Body weight (kg)	41.0 \pm 10.6	42.2 \pm 10.6	39.4 \pm 9.3	41.0 \pm 10.1	38.7 \pm 9.3	40.2 \pm 9.4	42.6 \pm 9.6	44.2 \pm 9.8
BMI (kg·m⁻²)	19.2 \pm 3.5	19.3 \pm 3.3	18.5 \pm 3.2	19.2 \pm 4.5	18.0 \pm 3.8	18.6 \pm 2.8	20.3 \pm 3.7	20.5 \pm 3.9
BMI (z-)	0.3 \pm 1.2	0.4 \pm 1.0	0.1 \pm 0.9	0.2 \pm 1.0	0.2 \pm	0.2 \pm 0.8	0.7 \pm	0.8 \pm

score)					1.0		0.9	1.0
WC (cm)	62.8 ± 8.1	67.2 ± 8.0	62.0 ± 7.5	61.7 ± 5.6	65.4 ± 7.5	61.9 ± 5.8	64.3 ± 7.6	65.8 ± 7.2
W/H (cm²)	0.8 ± 0.0	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.0	0.8 ± 0.1	0.8 ± 0.0	0.8 ± 0.0	0.8 ± 0.0
SBP (mmHg)	105.4 ± 9.6	108.1 ± 10.4	113.7 ± 16.8	107.7 ± 9.8	111.7 ± 11.7	106.6 ± 10.6	114.3 ± 10.7	111.6 ± 7.4
DBP (mmHg)	65.7 ± 7.5	64.5 ± 5.5	66.4 ± 8.2	63.5 ± 6.1	67.2 ± 5.5	63.3 ± 6.1	70.1 ± 7.1	70.1 ± 4.8
RHR (bpm)	87.2 ± 10.6	82.6 ± 12.8	92.0 ± 14.1	79.2 ± 10.2	92.7 ± 13.3	80.3 ± 10.3	91.3 ± 11.9	85.2 ± 8.9
SI (m·s⁻¹)	6.2 ± 1.2	6.3 ± 1.3	5.7 ± 1.4	6.2 ± 0.9	5.5 ± 1.3	6.2 ± 0.7	6.6 ± 1.2	6.4 ± 1.6
VO₂peak (ml·kg⁻¹·min⁻¹)	11.6 ± 5.1	14.8 ± 6.6	14.1 ± 7.3	20.5 ± 7.2	17.8 ± 9.8	22.8 ± 11.3	12.6 ± 6.8	15.9 ± 7.9
CRP (mg·L)	2.3 ± 2.3	1.9 ± 2.5	3.0 ± 2.8	1.0 ± 1.0	3.9 ± 8.7	1.0 ± 1.9	4.2 ± 5.6	2.3 ± 4.7
FG (mmol·L)	4.7 ± 0.8	4.3 ± 0.6	4.5 ± 0.5	4.1 ± 0.4	4.5 ± 0.6	4.4 ± 0.5	4.7 ± 0.5	4.6 ± 0.4
FINS (uU·mL)	16.5 ± 14.5	17.3 ± 14.7	8.8 ± 7.1	13.4 ± 9.4	10.7 ± 9.4	12.2 ± 7.9	17.9 ± 8.7	15.4 ± 13.1

BMI: body mass index; WC: waist circumference; W/H: waist-to-hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; RHR: resting heart rate; SI: stiffness index; VO₂peak: maximal aerobic capacity; CRP: c-reactive protein; FG: fasting glucose; FINS: fasting insulin.

Despite of the slight increase in body weight observed in all groups, the two-way ANOVA with repeated measures revealed significant and superior reductions for WC after the HIIT + MICT intervention (ES = -0.5; $p < 0.0001$) compared to the HIIT intervention (ES = -0.1), no improvement was noted in the MICT group. In accordance with these results, waist-to-hip ratio (WHR) was also significantly reduced in the HIIT + MICT group (ES = -0.8; $p < 0.0002$) compared with the HIIT group (ES = -0.2) and with no improvement found in the MICT group.

VO₂peak ($p < 0.0001$) significantly improved in all groups after 5-weeks of training with a trend towards an increase following the HIIT (ES = 0.9), the MICT (ES = 0.5) and the HIIT + MICT (ES = 0.5) groups.

There was a trend towards reduced SBP observed after both the HIIT (-6.1 ± -7.0 mmHg; ES = -0.5) and the HIIT + MICT (-5.1 ± -1.2 mmHg; ES = -0.5) interventions. No improvement was found for SBP in the MICT intervention. A significant reduction in DBP ($p = 0.0082$) was observed across all groups with no significant difference between groups.

Exercise-related reductions were noted for FG ($p = 0.0004$) across all groups with a trend towards improvement seen in the HIIT (ES = 0.9), the MICT (ES = 0.6) and the HIIT + MICT (ES = 0.1) groups. FINS did not improve in any group after 5-weeks of training. CRP was significantly lower after training ($p = 0.0016$) in all groups, showing a trend towards reduction after the HIIT (ES = -1.1), the MICT (ES = -0.2) and the HIIT + MICT (ES = -0.6) interventions.

Resting heart rate (RHR) was significantly reduced after training ($p < 0.0001$) with a trend towards reduction observed after the HIIT (-14.0%; ES = 1.1), the HIIT + MICT (-13.4%; ES = 1.1) and the MICT (-5.3%; ES = 0.4) interventions.

There was no significant change in SI in any of the groups following 5-weeks of training.

6.5 DISCUSSION

The purpose of this study was to evaluate the impact of short-term exercise of varying intensity on traditional CMD risk factors. The main findings of this study indicate that both short-term HIIT and MICT interventions are associated with significant improvements in most CMD risk factors (VO₂peak, RHR, FG, CRP) with slightly greater improvements observed in the HIIT group. Furthermore, the combined (HIIT + MICT) intervention was superior to HIIT and MICT interventions for reducing obesity indicators (WC, WHR).

Pediatric research has established the ability of both HIIT and MICT interventions to effectively improve cardiometabolic risk factors, however, fewer studies have

compared the different effects of HIIT and MICT (Sperlich et al., 2011; Racil et al., 2013; Dias et al., 2017) and to date, no study has examined the combined effects of HIIT and MICT.

Low levels of cardiorespiratory fitness in children have been associated with an increased risk for developing cardiometabolic disease later in life (Carnethon et al., 2003). Pediatric studies have reported superior improvements in VO_{2peak} and aerobic capacity using HIIT compared with MICT (Sperlich et al., 2011; Dias et al., 2017). Sperlich et al. (2011) compared the effects of 5-weeks HIIT (~90% MHR) versus MICT (60 – 75% MHR) among 19 adolescents (13.5 ± 0.4 y). The HIIT group significantly increased VO_{2max} with no significant change reported in the MICT group. A study exploring the different impact of HIIT (85 – 95% MHR) and MICT (60 – 70% MHR) over 12-weeks in 99 children (7-16 y) revealed greater VO_{2peak} in the HIIT group (Dias et al., 2017). The results from the current study show significant improvement in VO_{2peak} following HIIT, MICT and HIIT + MICT interventions. Although not significantly different between groups, improvement in VO_{2peak} was superior in magnitude following the HIIT intervention (ES = 0.9) compared with the MICT (ES = 0.5) and the HIIT + MICT (ES = 0.5) interventions. In addition, two studies have demonstrated a strong correlation between cardiorespiratory fitness and cardiac autonomic control (RMSSD) in children (Michels et al., 2013; Gutin et al., 2005).

WC and WHR are indicators of central obesity and have been recognized as independent predictors of CMD risk factors in children (Kelishadi, Mirmoghtadaee, Najafi, & Keikha, 2015). A comparison study showed that 12-weeks of HIIT set at an intensity of 100 – 110% of maximal aerobic speed (MAS) induced superior reductions in WC (-3.4 cm) compared with moderate intensity interval training (MIIT, 70 – 80% MAS; -3.0 cm) (Racil et al., 2013). Again in 2016, the latter HIIT protocol led to greater improved WC among 47 adolescents (14.2 ± 1.2 y) compared with the MIIT group (Racil et al., 2016). Results from previous studies indicate greater effects of HIIT over MICT on improving obesity indicators; however, the present study showed that HIIT + MICT reduced WC by -3.5 cm and may be more effective than HIIT (-0.3 cm) alone.

Regular exercise is known to improve arterial stiffness, however research exploring exercise interventions of shorter duration are limited. A recent study found that

12-weeks of HIIT improved arterial stiffness as measured by brachial-ankle pulse wave velocity (baPWV) in 48 obese children (8 -12 y) (Napasakorn, Daroonwan, & Hirofumi, 2018). Likewise, a meta-analysis involving 219 overweight and obese children showed enhanced vascular function (flow-mediated dilation) following exercise interventions ranging from 6 to 12 weeks (Dias, Green, Ingul, Pavey, & Coombes, 2015). In contrast to these findings, 5-weeks of exercise training in the present study was not associated with significant improvement in SI. The studies (Napasakorn et al., 2018; Dias et al., 2015) that have reported exercise-induced reduction in arterial stiffness involved overweight and obese children, this may suggest that exercise training may reverse arterial stiffness in overweight/obese children but have little effect on normal vascular structure assumed in healthy weight children used in the current study.

The participants in this study included both girls and boys, this may be a limitation as previous research has indicated different exercise effects by sex (Martínez-Vizcaíno et al., 2014). The interventions used in this study were restricted to aerobic activities that may limit the assumptions made in this study. Furthermore, the lack of controlling for diet and other activities outside of the intervention may have contributed to the findings from this study. Finally, the participants were not randomly assigned to the groups which could have made an impact on the results.

6.6 CONCLUSION

The findings from this study indicate that HIIT and MICT are both effective for improving cardiometabolic health in children. Improvements were greater in magnitude with some values following the HIIT intervention. A combination of HIIT and MICT may induce superior reductions in central obesity indicators. This suggests that the inclusion of both MICT and HIIT may be useful for improving central obesity, while, HIIT may be a time-efficient strategy to improve cardiometabolic health in children.

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CHAPTER 7: PAPER 5

Short-term High Intensity Interval Training is Superior to Moderate Intensity Continuous Training in Improving Cardiac Autonomic Function in Children

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7.1 ABSTRACT

Purpose This study aimed to investigate the impact of three isocaloric exercise programs on cardiac autonomic nervous system (ANS) functioning in children. **Methods** One hundred-and-nine children (39% boys; 61% girls) aged 10 to 13 years (11.07 ± 0.81 y) were conveniently assigned into one of four groups; 1. moderate intensity continuous training (MICT; $n = 29$) at 65% – 70% predicted maximum heart rate (MHR); 2. high intensity interval training (HIIT; $n = 29$) at > 80% predicted MHR; 3. HIIT and MICT combined on alternate weeks (ALT; $n = 27$) and 4. control group (CT; $n = 24$). Morning ANS activity was assessed using analysis of heart rate variability (HRV), supine for 10 min, pre and post the exercise intervention. A two-way analysis of variance was used to evaluate the effects of training on all HRV parameters ($p < 0.05/4 = 0.0125$). **Results** After 5-weeks of training, significant improvements were observed for $\ln\text{SDNN}$ ($p < 0.0001$), $\ln\text{RMSSD}$ ($p < 0.0001$) and $\ln\text{SD1}$ ($p < 0.0001$) with superior results reported in the HIIT group ($\text{ES} = 2.22$, $\text{ES} = 2.69$; $\text{ES} = 2.69$) compared with the MICT ($\text{ES} = 1.67$, $\text{ES} = 1.75$; $\text{ES} = 1.75$) and ALT ($\text{ES} = 0.87$, $\text{ES} = 1.06$; $\text{ES} = 1.06$) groups, respectively. **Conclusion** Short-term HIIT seems to induce superior alterations in cardiac ANS activity compared to MICT and ALT in children through enhanced vagal activity.

Keywords: cardiometabolic disease prevention, exercise, cardiac autonomic nervous system

7.2 INTRODUCTION

Insufficient physical activity (PA) is a global epidemic estimated to contribute to 5.3 million deaths (Lee et al., 2012). Sedentary lifestyles are not only increasing among adults but also in children, with global report cards on PA indicating a worldwide trend of children not participating in enough PA (Katzmarzyk et al., 2016; Maddison et al., 2016; Uys et al., 2016). PA levels are known to influence cardiac autonomic function, and is a possible mechanism for explaining the association between insufficient PA, morbidity and mortality. Cardiac autonomic dysfunction characterized by reduced parasympathetic (vagal) tone has been reported in children with low levels of habitual PA (Gutin, Barbeau, Litaker, Ferguson, & Owens, 2000).

Heart rate variability (HRV) provides insight into cardiac autonomic function by quantifying both vagal and sympathetic innervations of the heart (Task Force of the European Society of Cardiology, 1996). The magnitude of variability is measured in milliseconds and is derived from the mean and standard deviation of normal-to-normal interbeat intervals (IBI; SDNN). Subsequently, high variability is associated with increased vagal tone and effective cardiac autonomic function, while reduced HRV is a marker of cardiac autonomic dysfunction associated with increased sympathetic activity or reduced vagal activity (Dewland, Androne, Lee, Lampert, & Katz, 2007).

PA interventions have shown to improve cardiac autonomic function in both adults and children (Sandercock, Bromley, & Brodie, 2005; Bond et al., 2015). An adult meta-analysis of 13 studies has shown that the IBI length and high frequency band (HF) of spectral analyses increases by performing aerobic exercises (Sandercock et al., 2005). Pediatric research suggests that the same holds true for children. Nagai et al. (2004) investigated the cardiac autonomic effect of a 12-month moderate PA program (130 – 140 bpm; 20-min for 5 days/wk) in children (6 – 11 y) that had initial low HRV. Significant increases were reported for all HRV frequency domain components (LF, HF and TP) suggesting that moderate intensity exercise may improve both sympathetic and vagal nervous system activities (Nagai, & Moritani, 2004). Another study in the UK showed enhanced RMSSD in thirteen adolescents after two weeks of high intensity exercise (Bond et al., 2015). Moreover, the findings of Radtke et al. (2013) revealed

that adolescents (14.5 ± 0.7 y) engaging in higher amounts of moderate-to-vigorous PA (MVPA) (3000 – 5200 cpm) had favorable RMSSD values compared with those attaining lower amounts of MVPA.

Despite the available evidence linking exercise training with enhanced autonomic nervous system (ANS) activity in children, the exact dosage of exercise required for optimal ANS adaptation is unclear. To this end, the current study sought to examine the impact of three different isocaloric exercise protocols on cardiac autonomic modulation in children.

7.3 METHODS

Participants

One hundred-and-twenty children (11.07 ± 0.81 y) were recruited from two primary schools in KwaDlangezwa, KwaZulu-Natal, South Africa. The inclusion criteria required participants to be between the ages of 10 to 13 years old with no known clinical evidence of cardiovascular disease or any medical condition that would limit exercise training.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Study Design

This quasi-experimental study was approved by the KwaZulu-Natal Department of Education Institution (reference number 2/4/8/815) and cleared for ethics by the institution's Research Ethics Committee (UZREC171110-030). Data collection occurred between April and June 2016. An overview of the study design is shown in Figure 1.

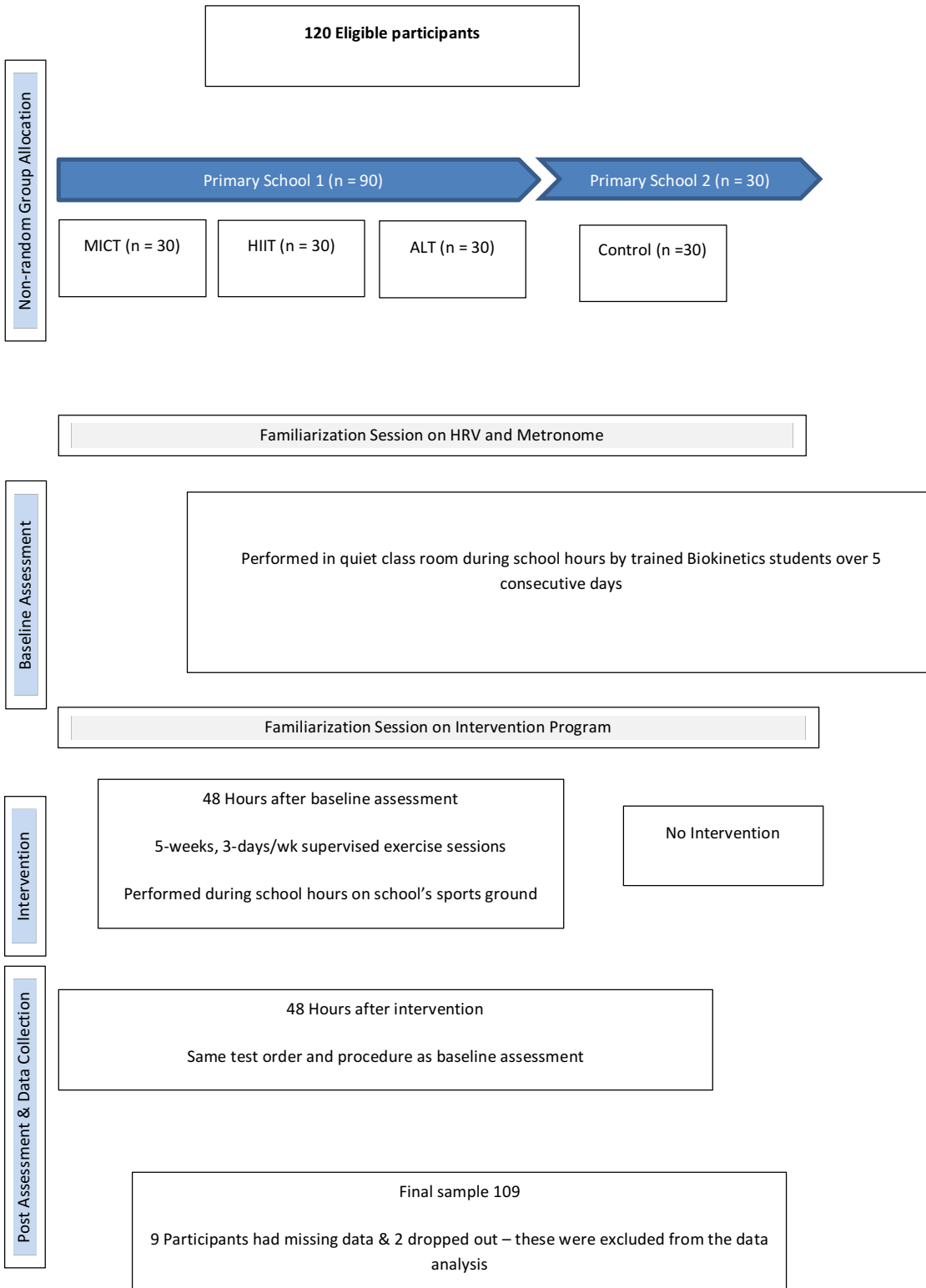


Figure 1: Overview of Study Design

Heart Rate Variability

Interbeat intervals (IBI) were recorded with the Suunto t6 monitor system using a chest belt that transmits data to a wrist watch (Suunto Inc; Vantaa, Finland). This device has been validated against an ambulatory five-lead electrocardiogram system and the Polar S810i chest belt system in adults (Weippert et al., 2013). The later has been validated and used in pediatric studies (Michels et al., 2013; Gamelin, Baquet, Berthoin, & Bosquet, 2008).

Morning HRV measurements were obtained pre and post the exercise intervention over 4 consecutive days with the first session starting at 7:30 AM and the last session at 11:30 AM. Participants had a familiarization session prior to the first day of testing. Data were collected in groups of four as permitted by the availability of equipment. Participants were required to lie supine for 10 minutes with the final 5 minutes being recorded (Task Force of the European Society of Cardiology, 1996). A metronome (15 breaths/min; 0.25 Hz) was used to guide normal regular pediatric respiratory rates (14-16 breaths/min) as well as minimizing external distraction during the 5-min recordings (Bar-Or, & Rowland, 2004). Pediatric studies have employed metronome-guided protocols during short term recordings of HRV (Kaufman, Kaiser, Steinberger, & Dengel, 2007; Winsley, Armstrong, Bywater, & Fawcner, 2003).

Following data collection, IBI were transferred from the Suunto t6 monitor system to excel and notepad. In notepad, the raw IBI series were screened for artefacts, removed and replaced with the mean of the adjacent beats. Further data processing was analyzed with Kubios HRV software (Biosignal Analysis and Medical Imaging Group, Joensuu, Finland). The HRV time domain indices obtained were IBI, standard deviation of normal-to-normal intervals (SDNN), root mean square of successive difference (RMSSD), count and percentage of adjacent IBI greater than 50 ms (NN50; pNN50). Power spectral analysis were performed using fast Fourier transformation (FFT) and autoregressive (AR) spectrums. Low frequency power band (LF: 0.04 - 0.15 Hz), high frequency power band (HF: 0.15 - 0.4 Hz) and LF/HF ratio were considered. The AR spectrum is documented as the preferred method for analyzing short-term recordings (providing greater resolution and decomposition) and is reported to be more sensitive to the effects of exercise (Mendonca, Fernhall, Heffernan, & Pereira, 2009).

Non-linear data were determined from the Poincare plot and included standard deviation 1 and 2 (SD1; SD2).

Physical Activity Levels

A modified version of the self-administered Physical Activity Questionnaire for Older Children (PAQ-C) was used to measure physical activity levels. The questionnaire measures general PA levels in children aged between 8 to 14 years old during a typical week in a school year. The survey includes 9-questions based on a broad spectrum of different activities taking place during physical education, first and second breaks, days and evenings and over the weekend. These questions were scored on a 5-point Likert rating scale assessing frequency and intensity of activities. A final mean score categorized children as having low, moderate, or high PA levels. Low levels of PA were scored between 1.00 - 2.33, moderate levels ranged from 2.34 - 3.66, and high levels ranged from 3.67 - 5.00 (Kowalski, Crocker, & Donen, 2004). Participants were requested not to change PA levels during the 5-week intervention period.

Resting Blood Pressure

Blood pressure was assessed utilizing a digital automated blood pressure device, Welch Allyn Connex® ProBPTM 3400 (Skaneateles Falls, NY 13153-0220, USA). This device meets the requirements of the Association for the Advancement of Medical Instrumentation (AAMI) standard (Alpert, 2007).

Participants were instructed to sit quietly on a chair for 5 minutes before taking two measurements. The average value of these measurements were recorded in millimetres of mercury (mmHg). A third measurement was taken and recorded for deviations beyond 5 mmHg between first and second measurements.

Body Mass Index

Participants' stature and body mass were measured with a stadiometer and a digital metric scale to the nearest 0.1 cm and 0.1 kg respectively. BMI-z scores were calculated for all participants.

Exercise Interventions

Participants were assigned to either moderate intensity continuous training (MICT), high intensity interval training (HIIT), alternative exercise training (ALT) or control group (CG) in a non-random fashion over 5-weeks (Figure 1). Participants were required to wear a Suunto M1 heart rate monitor (Suunto Oy, Finland) and were not allowed to consume any beverages during the exercise sessions. A one-day familiarization session, prior to the exercise intervention, was performed to acquaint participants with using their heart rate monitor and ensuring that their heart rate remains within the targeted range. A 5-minute warm up and cool down consisted of jogging at a low intensity followed with static stretching in all exercise sessions, data were not recorded during these periods. The mean energy expenditure over 15 sessions for the three respective groups were 154.29 ± 8.74 kcal (MICT), 156.00 ± 6.59 kcal (HIIT) and 154.19 ± 4.99 kcal (ALT).

1. MICT Participants completed thirty-three minutes of continuous brisk walking at an intensity of 65% -70% of their predicted MHR measured at baseline (target heart rate set between 135.85 - 146.30 bpm). The mean heart rate across all 15 sessions was 140.34 ± 4.23 bpm.

2. HIIT Participants were required to complete 10 x 60 s interval runs set at an intensity of > 80% of their predicted MHR measured at baseline (target heart rate set at > 167.20 bpm) separated with 75 s of active rest that entailed walking backwards (< 70% MHR) (Little, Safdar, Wilkin, Tarnopolsky, & Gibala, 2010). Each session lasted 23 minutes and produced a mean heart rate of 169.53 ± 3.84 bpm.

3. ALT Alternating weekly sessions of HIIT (169.00 ± 3.01 bpm) and MICT (140.22 ± 1.96 bpm) resulted in three non-consecutive weeks of HIIT (9 sessions in total) and two non-consecutive weeks of MICT (6 sessions in total). Participants recorded a mean heart rate of 157.49 ± 14.81 bpm across 15 sessions.

4. CT The control group were not exposed to any exercise intervention.

Statistical Analysis

Data are presented as arithmetic means \pm standard deviations unless otherwise stated. A two-way analysis of variance with repeated measurements was used to

evaluate group by time interactions and effects of group or time on all variables ($p < 0.05/4 = 0.0125$). Effect sizes (ES) were calculated to assess the magnitude of the difference and the values were interpreted as follows: > 0.8 is a large, 0.5 is a medium and < 0.2 is a small effect (Cohen, 1988). Normality for HRV variables were assessed by time (pre test and post-test) with the Kolmogorov-Smirnov test. Log-transformation was used to normalize variables with skewed distribution (lnIBI, lnSDNN, lnRMSSD, lnNN50, lnPNN50, lnSD1, lnSD2, lnLF, lnHF, lnLF/HF, on FFT and AR for all).

7.4 RESULTS

The final sample of this study included one hundred-and-nine ($n = 109$) participants consisting of 42 boys and 67 girls. The mean age was 11.07 ± 0.81 y. There were no between group differences in body weight ($p = 0.50$) and BMI z-scores ($p = 0.12$) therefore, excluding the possibility that these factors had influenced HRV as shown in previous pediatric studies (Table 1) (Farah, Ritti-Dias, Balagopal, Hill, & Prado, 2014; Lira et al., 2012; Lucini et al., 2013). Compliance within the exercise intervention groups were 96%, 95% and 92% for MICT, HIIT and ALT, respectively. Participants in the ALT group recorded significantly greater self-reported PA after 5-weeks ($+ 30\%$; $p < 0.0001$; $ES = 1.34$) compared with participants in the HIIT ($+ 6.88\%$; $ES = 0.328$) and MICT ($+ 10.50\%$; $ES = 0.592$) groups (Table 1). PA levels revealed additional significant interactions in group ($p < 0.001$) and time ($p < 0.001$) indicating group differences in subjective PA levels at both pre to post intervention.

Table 1. Exercise Intervention Effects on Physical Characteristics and Physical Activity Levels

Variable	MICT (n = 29)		HIIT (n = 29)		ALT (n = 27)		CG (n = 24)	
	M \pm SD		M \pm SD		M \pm SD		M \pm SD	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
BW (kg)	41.02 \pm 10.61	42.15 \pm 10.62	39.41 \pm 9.25	40.98 \pm 10.11	38.74 \pm 9.32	40.20 \pm 9.35	42.58 \pm 9.56	44.17 \pm 9.84
BMI (z-)	0.29 \pm	0.36 \pm	0.12 \pm	0.17 \pm	0.15 \pm	0.23 \pm	0.70 \pm	0.76 \pm

score)	1.15	1.01	0.93	1.04	1.01	0.77	0.90	0.97
SBP (mmHg)	105.40 ± 9.56	108.05 ± 10.44	113.72 ± 16.78	107.66 ± 9.79	111.74 ± 11.74	106.63 ± 10.59	114.27 ± 10.66	111.58 ± 7.36
DBP (mmHg)	65.67 ± 7.45	64.47 ± 5.48	66.38 ± 8.18	63.50 ± 6.10	67.15 ± 5.52	63.31 ± 6.05	70.08 ± 7.12	70.08 ± 4.77
RHR (bpm)	87.24 ± 10.56	82.62 ± 12.75	92.03 ± 14.13	79.24 ± 10.18*	92.67 ± 13.33	80.26 ± 10.26*	91.33 ± 11.90	85.15 ± 8.92
PAQ-C	2.76 ± 0.50	3.05 ± 0.48	2.76 ± 0.54	2.95 ± 0.62	2.21 ± 0.68	3.05 ± 0.57*	2.28 ± 0.73	2.25 ± 0.37

BW: body weight; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; RHR: resting heart rate; PAQ-C: physical activity questionnaire for older children. * group x time interaction ($p < 0.05$; $ES > 0.8$).

There was a significant time effect ($p = 0.02$) for systolic blood pressure (SBP), with a large decrease of 5.33% in the HIIT group (113.72 ± 16.78 mmHG to 107.66 ± 9.79 mmHG; $ES = 0.46$). There was a significant time effect ($p < 0.0001$) for resting heart rate (RHR), with the HIIT and ALT groups improving the most, by -13.90% ($ES = -1.05$) and -13.39% ($ES = -1.05$), respectively (Table 1).

Time Domain Parameters of HRV

All time domain HRV parameters ($\ln IBI$, $\ln SDNN$, $\ln RMSSD$, $\ln NN50$ and $\ln pNN50$) showed main effects for time ($p < 0.0001$). The 2-way ANOVA with repeated measures revealed a significant group x time interaction for $\ln IBI$ ($p < 0.0001$) after 5-weeks of training. The effect was greater after the HIIT intervention ($ES = 2.94$) versus the MICT ($ES = 2.39$) and ALT ($ES = 1.63$) interventions (Table 2).

Table 2. Exercise Responses on lnIBI, lnSDNN, lnRMSSD and lnSD1

Variable	MICT (n = 29)		HIIT (n = 29)		ALT (n = 27)		CG (n = 24)	
	M ± SD		M ± SD		M ± SD		M ± SD	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
lnIBI (ms)	6.36 ± 0.09	6.62 ± 0.12	6.38 ± 0.09	6.72 ± 0.13	6.43 ± 0.13	6.68 ± 0.14	6.47 ± 0.13	6.56 ± 0.12
lnSDNN (ms)	3.08 ± 0.44	4.01 ± 0.51	3.18 ± 0.56	4.33 ± 0.42	3.49 ± 0.55	4.00 ± 0.43	3.59 ± 0.51	3.99 ± 0.55
lnRMSSD (ms)	2.59 ± 0.68	4.05 ± 0.63	2.69 ± 0.89	4.45 ± 0.45	3.16 ± 0.87	4.08 ± 0.50	3.54 ± 0.75	3.99 ± 0.72
lnSD1 (ms)	2.25 ± 0.68	3.70 ± 0.63	2.34 ± 0.89	4.11 ± 0.45	2.81 ± 0.87	3.74 ± 0.50	3.19 ± 0.75	3.65 ± 0.72

ln: Log transformation of data; IBI: interbeat interval; SDNN: standard deviation of normal-to-normal interbeat intervals; RMSSD: root means square of successive differences; SD1: standard deviation 1 on Poincare plot.

Significant interactions were observed for lnSDNN ($p < 0.0001$) after training with a larger mean increase achieved in the HIIT group (55.16 ± 20.50 ms; ES = 2.22) versus the MICT (38.91 ± 24.11 ms; ES = 1.67) and ALT (21.73 ± 3.65 ms; ES = 0.87) groups. For lnRMSSD, significant interactions (group x time) were observed post training ($p < 0.0001$), the effectiveness of training was greater in the HIIT group (ES = 2.69) compared with the MICT (ES = 1.75) and ALT (ES = 1.06) groups. Finally, no significant group x time interactions were observed for both lnNN50 and lnnpNN50.

Frequency Domain Parameters of HRV

Spectral analysis revealed significant time effects from baseline to post intervention for lnLF, lnHF and lnLF/HF on both FFT and AR spectrums ($p < 0.0001$ for both spectrums) (Table 3).

Table 3. Exercise Intervention Effects on lnLF, lnHF and lnLF/HF

	MICT (n = 29)		HIIT (n = 29)		ALT (n = 27)		CG (n = 24)	
	M ± SD		M ± SD		M ± SD		M ± SD	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
lnLF (nu)								
FFT	4.07 ± 0.36	3.34 ± 0.67	3.91 ± 0.47	3.49 ± 0.48	4.03 ± 0.31	3.42 ± 0.57	3.59 ± 0.64	3.47 ± 0.73
AR	4.05 ± 0.33	3.40 ± 0.64	3.92 ± 0.43	3.46 ± 0.44	3.97 ± 0.31	3.45 ± 0.47	3.64 ± 0.54	3.48 ± 0.60
lnHF (nu)								
FFT	3.51 ± 0.48	4.15 ± 0.29	3.60 ± 0.71	4.10 ± 0.26	3.61 ± 0.46	4.10 ± 0.40	3.93 ± 0.48	3.98 ± 0.49
AR	3.58 ± 0.42	4.12 ± 0.26	3.67 ± 0.56	4.15 ± 0.19	3.71 ± 0.40	4.14 ± 0.25	3.96 ± 0.38	4.06 ± 0.36
lnLF/HF								
FFT	0.56 ± 0.83	-0.81 ± 0.94	0.31 ± 1.14	-0.61 ± 0.72	0.42 ± 0.76	-0.67 ± 0.93	-0.31 ± 1.12	-0.50 ± 1.19
AR	0.46 ± 0.74	-0.72 ± 0.89	0.25 ± 0.97	-0.68 ± 0.62	0.26 ± 0.70	-0.68 ± 0.72	-0.31 ± 0.91	-0.57 ± 0.94

ln: Log transformation of data; LF: low frequency; HF: high frequency; LF/HF: low frequency and high frequency power ratio; FFT: fast Fourier transform spectrum; AR: autoregressive spectrum.

Significant group x time interactions were reported post training for lnHF on both FFT ($p = 0.0061$) and AR ($p = 0.0036$) spectrums. The effect of training on lnHF power was larger following the MICT intervention ($ES = 1.61$; $ES = 1.50$) compared with the HIIT ($ES = 0.97$; $ES = 1.22$) and ALT ($ES = 1.33$; $ES = 1.34$) interventions for both FFT and AR spectrums, respectively. lnLF decreased across all groups after training and showed significant group x time interactions on the FFT spectrum ($p = 0.0087$). The decline was larger following the MICT intervention ($ES = -1.61$) compared with the HIIT ($ES = -0.99$) and ALT ($ES = -1.33$) interventions on the FFT spectrum.

A significant group x time interaction for lnLF/HF ratio was found on both FFT and AR spectrums ($p = 0.0055$; $p = 0.0047$), respectively. Most improvement was observed in the MICT group ($ES = -1.56$; $ES = -1.54$) compared with the HIIT ($ES = -0.85$; $ES = -1.21$) and ALT ($ES = -0.85$; $ES = -1.24$) groups, respectively.

Nonlinear Parameters of HRV

The nonlinear parameter lnSD1 revealed a significant group x time interaction ($p < 0.0001$) with a greater response in the HIIT group ($ES = 2.69$) compared with MICT ($ES = 1.75$) and ALT ($ES = 1.06$) groups. A significant time difference was observed for lnSD1 ($p < 0.0001$). However, no significant group difference was observed in any HRV parameter.

7.5 DISCUSSION

The aim of this study was to examine the impact of different exercise protocols on cardiac ANS function in children. The key findings from this study indicate that exercise-induced alterations in the cardiac ANS is intensity-dependent. High intensity (HIIT) provoked superior variability through enhanced vagal activity (IBI, SDNN, RMSSD, SD1). Whereas, moderate intensity (MICT) induced most improvement in sympathovagal balance (LF/HF) characterized by increased vagal activity (HF). Combined intensities (HIIT + MICT = ALT) had no additional benefits in cardiac ANS functioning, however self-reported PA levels showed largest improvements following this intervention.

To date, the majority of pediatric research has exclusively considered the impact of either moderate intensity exercise or high intensity exercise on cardiac ANS activity. Despite the lack of research, improved vagal activity has been reported to occur with higher exercise intensity in children (Gutin et al., 2000; Bond et al., 2015). Favorable changes in RMSSD (6.10 ± 27.80 ms) was observed among seventy-nine obese children (7 to 11 y) following a 40-min exercise intervention that produced an average heart rate of 157 bpm (Gutin et al., 2000). The latter study compared its clinical significance with Stein, Rottman and Kleiger's (1996) findings on smokers (23 – 69 y) that quit smoking and increased RMSSD from 30 to 35 ms. Two-weeks of HIIT was reported to improve RMSSD (58.30 ± 19.10 ms to 65.20 ± 30.80 ms) among thirteen normal weight children (13 to 14 y). RMSSD remained significant after 3-days (62.90 ± 24.0 ms) (Bond et al., 2015). The protocol entailed 8-10 x 1-min intervals at 90% peak power output separated with 75 s active rest (Bond et al., 2015). In contrast to the

findings of these studies and the current study, Gamelin et al. (2009) found no significant difference for any of the HRV parameters (SDNN, RMSSD, LF, HF, SD1 and SD2) after 7-weeks of high intensity exercise among 38 children (9.6 ± 1.2 y). The training protocol entailed maximal (100% of MAV) and supra-maximal (190% of MAV) aerobic velocities (MAV). The authors concluded that the exercise intensities might have led to a fatigued state which may explain the lack of significant changes in ANS (Gamelin et al., 2009).

Few studies have examined changes in frequency domain indices of HRV following exercise training among children. Two studies have demonstrated moderate intensity exercise to induce changes in frequency domain indices (Nagai et al., 2004; Mandigout et al., 2002). Nagai and Moritani (2004) observed increases in LF ($5.70 \pm 0.60 \text{ ms}^2 - 6.10 \pm 0.61 \text{ ms}^2$; $p < 0.001$), HF ($5.50 \pm 0.64 \text{ ms}^2 - 5.78 \pm 0.77 \text{ ms}^2$; $p < 0.01$) and TP ($6.33 \pm 0.50 \text{ ms}^2 - 6.71 \pm 0.57 \text{ ms}^2$; $p < 0.001$) in 100 children (6 – 11 y) with initial low HRV values (absolute value of TP $< 1000 \text{ ms}^2$ or TP ln < 6.80) following a 12-month moderate intensity program (130 – 140 bpm) (Nagai, & Moritani, 2004). In addition, a thirteen-week endurance training program (3 x 1 h week⁻¹; intensity, $> 80\%$ HR_{max}) elicited significant changes in HF ($3.1 \pm 0.3 \log \text{ m}^2$) and LF ($3.3 \pm 0.3 \log \text{ m}^2$) among 19 children (10 – 11 y) (Mandigout et al., 2002).

The current study is in line with these studies that observed favorable improvements in the HF component of HRV following a moderate intensity exercise protocol. When taking the latter into consideration, the results from the current study together with previous studies (Nagai, & Moritani, 2004; Mandigout et al., 2002), partly suggest that enhanced vagal tone (HF) may be stimulated by both acute and chronic moderate intensity exercise. However, results from the current study showed increases in mean SBP ($105.40 \pm 9.56 \text{ mmHg}$ to $108.05 \pm 10.44 \text{ mmHg}$) in the MICT group indicating that non-neural factors (i.e. mood, alertness, mental activity) may have contributed to the improved HF component of HRV (Task Force of the European Society of Cardiology, 1996). Furthermore, elevated SBP has been positively associated with increased WC, both observed within the MICT group (Choy et al., 2011). It is worth mentioning that the metronome protocol used in the present study may

have overlapped with the power band widths of spectral analysis, limiting the underlying assumptions.

This study employed a metronome-guided protocol (0.25 Hz) during HRV measurements that may have overlapped with HF heart rate fluctuations (0.15 - 0.4 Hz), reducing measurement reliability. However, there is much controversy regarding paced breathing and HRV, with a study reporting paced breathing to have no effects on HRV indices (Kox et al., 2011). Moreover, RMSSD, considered an index of vagal activity (Buchheit, 2014) has become very popular among researchers for field HRV analysis. Finally, it is possible that factors other than the exercise interventions may have attributed to enhanced HRV. For example, alterations in cardiac ANS has been associated with insulin resistance in adolescents (Cozzolino et al., 2015).

7.6 CONCLUSION

The present study provides evidence on exercise-induced improvements in cardiac ANS activity among children. Despite the effectiveness of HIIT, MICT and ALT interventions, the findings suggest that both the magnitude and components of the ANS relate to exercise intensity. When comparing the effects of these interventions, optimal variability (SDNN) and enhanced vagal activity (RMSSD, SD1) seem to be achieved through HIIT induced adaptations, while improved sympathovagal activity (LF/HF) characterized by increased vagal activity (HF) appears to respond best with MICT.

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CHAPTER 8: SUMMARY, CONCLUSIONS AND FUTURE STUDIES

This thesis aimed to identify PA levels and then explore different exercise interventions that may modify the risk for CMD in children from South African primary schools in urban areas. Five papers were produced to address these specific aims. The contributions made to the literature are detailed in table 1.

The following section will explain and discuss the implications of the findings from each paper.

8.1 PHYSICAL ACTIVITY LEVELS

Paper 1 highlighted discrepancies in PA levels among children in South Africa. The key findings from this paper indicated that:

- Girls, older children, other ethnicity groups and those residing in the Northern Cape province are at risk for accumulating insufficient PA.

PA discrepancies among genders and age groups have been ascribed to biological and maturation differences, respectively (Wickel, Eisenmann, & Welk, 2009; Craggs, Corder, van Sluijs, & Griffin, 2011). However, differences in PA levels related to gender have been reduced after the researchers adjusted for maturity (Telford, Telford, Olive, Cochrane, & Davey, 2016). This indicates that lower levels of PA in girls may be linked to girls' maturing at an earlier chronological age.

Paper 1 identified other ethnicity as the ethnicity group that participated in the lowest amount of PA. In 2016, provinces with the highest distribution of other ethnicity groups (defined as Coloured, Indian or Asian) were the Northern Cape province and the Western Cape province, and these groups constituted 44% and 48% of the provinces' populations, respectively (Statistics South Africa, 2016). In addition, the other ethnicity groups were found to participate in the lowest amounts of PA levels, as shown in Paper 1. Therefore, the high percentage of other ethnicity groups within the Northern Cape province partly explains the low PA levels but does not explain the high PA levels in the Western Cape province, which was one of the top three active provinces. This indicates

that in addition to ethnicity, there are other reasons that may explain the low PA levels observed in the Northern Cape.

Education level has been recognised as a major component of socioeconomic status (SES), which in turn influences PA levels (Marmot, 2005). Statistics South Africa (2016) has stated that the Northern Cape has the lowest rates of primary education, secondary education and higher degree education when compared with all other provinces. Adult studies have reported positive associations between education levels and PA levels (Shaw & Spokane, 2008; He & Baker, 2005). McAuley et al. (2006) have explained that a higher education level is linked to knowledge of PA health benefits and provides the resources needed to participate in PA. To date, there is no available data on adult PA levels in the Northern Cape. However, 51% of deaths were related to noncommunicable diseases that might have been connected to low PA levels (MRC, 2000). Last, parents' PA levels are directly linked to children's PA levels through role modelling and emphasising the importance of PA (Cools, De Martelaer, Samaey, & Andries, 2011). Furthermore, a study done by Huppertz et al. (2016) showed that the link between parental PA levels and children's PA levels may be explained by genetical factors. These findings and those of Paper 1 imply that children residing in the Northern Cape may have the lowest PA levels because their parents have low education levels. The results of Paper 1 raises important issues about inequalities in socioeconomics among provinces in South Africa; and opportunities to participate in PA among gender, age groups and ethnicities. The reported discrepancies in PA levels suggest that there may be health disparities among the same high-risk groups. However, this notion of health disparities is only speculative and requires research to examine the equity in health quality and care among South African children.

8.2 ASSOCIATIONS BETWEEN CMD RISK AND CARDIAC ANS

Low PA levels increase the risk for developing CMD, which has been associated with cardiac ANS dysfunction (Gutin, Barbeau, Litaker, Ferguson, & Owens, 2000). Few paediatric studies have investigated the connection between CMD risk factors and cardiac ANS dysfunction. One reason for this is the continuous debate for defining CMD

syndrome (also known as the metabolic syndrome) in children (Rodríguez-Colón et al., 2015). Research in paediatric cardiac ANS has been largely focused on determining independent links between BMI (Farah, Ritti-Dias, Balagopal, Hill, & Prado, 2014; Zhou, Xie, Wang, & Yang, 2012), WC (Paschoal, Trevizan & Scodeler, 2009; Zhou et al., 2012; Farah, Do Prado, Tenorio, & Ritti-Dias, 2013) and SBP (Farah et al., 2014; Xie et al., 2013). The connections found between cardiac ANS and CMD risk factors are consistent with Paper 2's results. Paper 2 showed that:

- Parasympathetic activity (RMSSD, pNN50, HF, SD1) is associated with CMD risk factors.

More specifically, a decrease in HDL and increases in LDL, WC, HC and FINS showed associations with parasympathetic withdrawal. The latter variables showed both dependent and independent associations with correlation and regression analyses, respectively. Significant correlations were found between the BMI z-score and RMSSD, but when the regression analysis was performed, no association was detected. This may indicate that the distribution of adiposity is a key determinant of cardiac ANS and that the BMI z-score does not adequately reflect the toxic effect of adiposity on cardiac ANS functioning. Moreover, an increase in WC, an indicator of central obesity, has been associated with low adiponectin serum levels, a protein hormone found to be involved in the breakdown of fatty acid and regulating glucose levels (Cnop et al., 2003), which in turn have been shown to positively correlate with HRV (Jung et al., 2012). Adiponectin has received much attention in the field of CMD because of its relation with insulin sensitivity, glucose disposal, lipid metabolism and the risk for developing CMD (Toth, 2005). A review study on 25 articles (which involved healthy adults and adolescents) has demonstrated that serum adiponectin levels are positively associated with HDL levels and negatively associated with LDL levels (Izadi, Farabad, & Azadbakht, 2013). Paper 2's findings are supported by research on adiponectin levels and its associations between HRV, HDL, LDL and WC. These results indicate the clinical relevance for screening HDL, LDL, WC, HC and FINS in predicting CMD risk among Black children.

A further important finding is the absence of significant correlations between the parasympathetic activity indices of HRV (RMSSD, pNN50, HF and SD1), SBP, DBP, FG and SI. Jaiswal et al. (2013) found similar results for RMSSD and PWV in healthy adults

when their results were compared with those of diabetic adults; RMSSD was not associated with PWV in healthy adults but in diabetic adults. The same was found for SBP and ANS in adolescence versus preadolescence (Tanaka et al., 2000). This may imply distinctive influence of CMD risk factors on ANS in different cohorts. In this case, it appears that SBP, DBP, FG and SI have little influence on ANS in apparently healthy black South African children aged 11.85 ± 0.89 years old. The findings from paper 2 foster questions about CMD and ANS that requires further investigation. Could the results be replicated in another sample? Could HRV be an alternative tool predicting CMD and replacing the practice of screening traditional risk factors in clinical settings? This may require further investigation in terms of the reliability and validity of HRV as a novel CMD risk factor among children of different ethnicities.

8.3 EXERCISE INTERVENTIONS ON REDUCING CMD

Paediatric PA guidelines (6–17 y) issued by the US Department of Health and Human Services (USDHHS) recommend 60 min of daily MVPA (USDHHS, 2008). However, these guidelines are vague and lack proper protocol for the prevention of CMD risk. Moreover, paediatric research has reported potent effects of vigorous PA on CMD risk (Keating, Johnson, Mielke, & Coombes, 2017). With these considered, Paper 3 investigated the effects of different exercise intensities on CMD risk factors. The findings from Paper 3 showed that:

- Moderate intensity and vigorous intensity exercise protocols induce separate cardiometabolic benefits.

This poses the question about whether combined intensities will produce optimal cardiometabolic improvements as proposed by USDHHS; and whether the benefits will be attainable in less than 60 min. This was explored further in Paper 4. Paper 3 also provided the novel concept of including a combined protocol of moderate and vigorous intensities on alternative weeks, which was used in Papers 4 and 5. Paper 4 examined the influence of short-term exercise of different intensity on CMD risk factors. The primary findings of Paper 4 indicated that:

- Short-term HIIT induce favourable cardiometabolic benefits compared with MICT and a combination of MICT and HIIT.

The magnitude of improvements in SBP, DBP, RHR, VO_2 peak, FG and CRP was higher following the HIIT intervention, when compared with the results of the MICT intervention and the combined MICT and HIIT intervention, though the improvements were not significant among the groups. The combined MICT and HIIT intervention significantly improved WC and WHR when compared with the MICT and HIIT interventions alone. Last, the MICT intervention led to increases in WC, WHR and SBP. These increases may be explained by factors outside the researcher's control (E.g. participants' diets). Furthermore, a cross sectional study found that moderate PA was effective for improving WC in younger children (6–9 y), while vigorous PA was required for the same in older children (9–15 y) (Dalene et al., 2017). The study concluded that the different effects of PA intensities can be explained by physiological and behavioural differences that can affect adiposity (Dalene et al., 2017). This finding is supported by Loprinzi, Cardinal, Lee, and Tudor-Locke (2015), who found no improvement for WC following moderate PA in 15-year-olds. Taken together, the results suggest that older children may require higher exercise intensities for optimal cardiometabolic benefits. This implies that PA guidelines should be age-specific. Moreover, no improvements were observed for FINS and SI in any of the groups. According to the findings of Paper 4, the use of HIIT is more effective in reducing CMD risk factors in children than are MICT or a combination of MICT and HIIT. The superior effects may be explained by a longitudinal study that reported a significant independent association between VO_2 peak and clustered CMD risk factors in children (6–11 y) (Zaqout et al., 2016). Though HIIT appears superior for inducing favourable cardiometabolic benefits, WC and WHR responded the best when a combination of MICT and HIIT interventions were applied. This holds valuable information on combatting childhood obesity and should be further explored in obesity studies. Another important result of this paper was that all exercise interventions led to certain cardiometabolic benefits in the presence of slight increases in weight and BMI. This implies that exercise interventions aimed at reducing CMD risk factors should not be focused on improving either body weight or BMI but instead aim to increase VO_2 peak. The results of Paper 4 lead to the questioning of the longstanding

utility of paediatric PA guidelines, in that it should perhaps be replaced with HIIT for optimal cardiometabolic benefits. Moreover, the use of HIIT also appears to be promising in altering cardiac ANS activity (Bond et al., 2015), however the effects of exercise intensity on ANS is inconclusive and was therefore explored in Paper 5. The results from Paper 5 demonstrated that:

- Parasympathetic activity are most enhanced following short-term HIIT.

The SDNN, RMSSD and SD1 were significantly higher in the HIIT intervention than in the MICT intervention and the combined MICT and HIIT intervention, suggesting a better parasympathetic tone. A retrospective study including 179 veterans showed that a 10 ms increase in SDNN was associated with a 20% decrease in mortality (Bilchick et al., 2002). Paper 5 reported mean changes for the HIIT group as 55.16 ± 20.50 ms, the MICT group as 38.91 ± 24.11 ms and the combined MICT and HIIT group as 21.73 ± 3.65 ms. Indeed, exercise has been proposed to hold cardioprotective benefits by reducing CMD risk factors and increasing parasympathetic tone (Oliveira, Barker, Wilkinson, Abbott, & Williams, 2017). However, the relationship between CMD risk factors and cardiac ANS tone is not well understood. Much debate exists in literature on whether exercise induces improvements in CMD risk factors, thereby leading to enhanced parasympathetic tone (Oliveira et al., 2017) or that exercise stimulates parasympathetic tone, thereby leading to improvements in CMD risk factors (Bond et al., 2015). Ordway, Charles, Randall, Billman, and Wekstein (1982) provided an example of the ability of exercise to induce changes in the cardiac autonomic tone. They showed that after an exercise intervention, dogs who had their autonomic nerves removed did not experience a reduction in RHR when compared with the control group. This may indicate that an enhanced HRV is attributable to exercise that leads to improvements in specific CMD risk factors. In Paper 5, increased parasympathetic activity was accompanied by significant improvements in RHR, VO_2 peak, FG and CRP following HIIT, MICT and the combination of MICT and HIIT. These reductions showed the most change following the HIIT intervention, indicating a superior enhancement of parasympathetic innervation.

The underlying mechanisms of HIIT relative to MICT to induce alterations to the cardiac ANS are limited in humans because of the difficulty of obtaining direct

measurements of ANS activity. Haram et al. (2009) reported that HIIT induced an enhanced sensitivity to acetylcholine in rats following 8 week of HIIT when compared with MICT. Similarly, according to Batacan, Duncan, Dalbo, Buitrago and Fenning (2018), HIIT stimulates parasympathetic activity by decreasing mesenteric artery contractile (sympathetic activity) responses to norepinephrine and by increasing mesenteric artery relaxation responses to acetylcholine (parasympathetic activity). The latter findings were based on a 12-week HIIT versus MICT intervention in rats. The authors concluded that HIIT appears to have a superior ability to suppress or block mesenteric α -adrenergic contractile responses and, as a result, enhance parasympathetic tone (Batacan et al., 2018).

Other mechanisms by which exercise groups enhanced parasympathetic activity may be explained by reductions reported in RHR and SBP. For example, changes in RHR are suggested to reflect direct alterations to the autonomic tone, with the parasympathetic tone slowing down the heart rate (Mann, Zipes, Libby, & Bonow, 2014). Though chronic BP is regulated by the endocrine system, enhanced parasympathetic activity may produce acute reductions in BP (Nederend, Schutte, Bartels, ten Harkel, & de Geus, 2016). The latter was observed in both the HIIT group and the combined MICT and HIIT group.

The absence of a significant correlation between SI (endocrine) and parasympathetic activity indices (Paper 2) may confirm that alterations in SBP caused by increased parasympathetic tone (Paper 5) are acute. Moreover, SI increased following all exercise interventions, indicating that prolonged exercises, as opposed to acute exercises, appear to be effective in altering structural changes to the endothelium. A meta-analysis in healthy young adults is consistent with the latter finding that indicates acute exercise is unable to alter arterial stiffness (Pierce, Doma & Leicht, 2018). Exercise may produce inflammatory products caused by muscle damage that has an adverse effect on nitric oxide bioavailability, hence explaining the increase in arterial stiffness (Vlachopoulos et al., 2005).

In relation to current paediatric PA guidelines, the findings of Papers 4 and 5 advocate the effectiveness of HIIT on both CMD risk factors and cardiac ANS tone.

Table 1. Contribution to Literature

Paper	Contribution	Limitations
1	Significant discrepancies in PA levels were found among genders, age groups, ethnicities and provinces.	Measures of PA are limited to self-reported participation.
2	CMD risk factors are linked to a withdrawal in parasympathetic activity.	Lack of control group.
3	Moderate and vigorous exercise intensities induce different cardiometabolic benefits.	Lack of control group and lack of caloric-matched comparison.
4	Short-term HIIT induce favourable cardiometabolic benefits compared with MICT and a combination of MICT and HIIT.	Long-term effects of exercise intensity on both CMD risk factors and cardiac ANS tone may result in different outcomes.
5	The magnitude of alterations in cardiac ANS activity is dependent on intensity. Enhanced parasympathetic activity may be induced following short-term HIIT.	

CMD: cardiometabolic disease; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; ANS: autonomic nervous system.

This thesis implemented a broad approach in first providing an overall view of PA levels in South Africa. This was followed by examining the relationship between CMD risk factors and cardiac ANS activity in children of black ethnicity, a first in literature. The explorative study on different exercise intensities was driven by the gaps in current paediatric PA guidelines that led to the development of the novel concept of combining moderate and vigorous intensities on alternative weeks. Last, this thesis contributes knowledge on the influence of exercise intensity on CMD risk and is the first South African study to report on the different effects of exercise intensities on cardiac ANS in children. The thesis also raised important question for future research. First, are there discrepancies in health among gender, age groups, other ethnicities and provinces in South Africa? Second, can HRV replicate the same predictive value of certain CMD risk factors in children of black ethnicity? Third, can long-term HIIT interventions reproduce superior cardiometabolic and cardiac ANS effects when compared to MICT?

In conclusion, the findings of this thesis give strong support for tailored PA programmes that match social, emotional and socioeconomic needs among youth in South Africa. The department of health should consider prescreening of CMD risk factors – schools may act as ideal settings to implement such interventions. Last, the departments of education and sport and recreation are encouraged to invest in HIIT as time-efficient PA strategies that will induce optimal cardiometabolic health benefits.

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**Ethics Committee
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University of Zululand**

C/O Dr L Vivier
Department of Zoology
University of Zululand
Private Bag 1001
KwaDlangezwa
3886
Tel: 035 – 902 6741
Email: lvivier@pan.uzulu.ac.za

17 January 2012

To whom it may concern

ETHICS EVALUATION OF RESEARCH PROJECT PROPOSAL

This letter serves to confirm that **Ms A van Biljon** registered for a **PhD Degree** in the **Department of Biokinetics and Sport Science**, Faculty of Science and Agriculture, at the University of Zululand, in accordance with appropriate rules, submitted a research project proposal to the Ethics Committee of the Faculty of Science and Agriculture. The research project will investigate: **Identification and modification of cardiometabolic disease risk factors in South African primary school children**. Based on the research protocol stipulated, the Ethics Committee of the Faculty of Science and Agriculture could find no reason from an ethical standpoint to reject the proposed research.

Yours sincerely

Dr L Vivier
Chairperson
Ethics Committee
Faculty of Science and Agriculture
University of Zululand



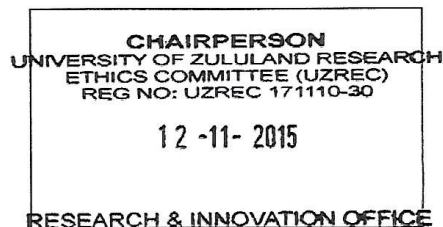
ETHICAL CLEARANCE CERTIFICATE

Certificate Number	UZREC 171110-030 PGD 2015/102						
Project Title	Identification and modification of cardiometabolic diseases risk factors in South African primary school children						
Principal Researcher/ Investigator	A van Biljon						
Supervisor and Co-supervisor	Prof. SJ Semple				Dr. J Grace Prof Kolanisi		
Department	Biokinetics & Sports Science						
Nature of Project	Honours/4 th Year		Master's	x	Doctoral	X	Departmental

Ms. Aneke van Biljon is a Doctoral candidate at the University of Zululand who has submitted her thesis for external examination. She registered his Doctoral degree in 2011 and collected data in 2012, at the time no formal procedures were in place for assessing ethical compliance. He then received a provisional ethical clearance at Faculty level which he then preceded collecting data.

Having considered the documents submitted to me and the methodology employed in conducting the research, I hereby certify, on behalf of the University of Zululand's Research Ethics Committee (UZREC), that the research complied with the University's research ethics requirements.

Professor Nokuthula Kunene
 Chairperson: University Research Ethics Committee
 12 November 2015



A van Biljon - PGD 2015/102

Physical Activity Questionnaire

Gender: M _____ F _____

Grade: _____

Age: _____

Race: _____

Province: _____

Teacher: _____

We are trying to find out about your level of physical activity from ***the last 7 days*** (in the last week). This includes sports or dance that make you sweat or make your legs feel tired, or games that make you breathe hard, like tag, skipping, running, climbing and other.

Remember:

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

1. Have you done any of the following activities in the past 7 days (last week)? If yes, how many times? Please mark one circle per row. If you did not do please indicate by NO.

	No	1-2 times	3-4 times	5-6 times	7-8 times
Skipping					
Netball					
Rowing/Canoeing					
Tennis					
Touchers					
Walking for exercise					
Bicycling					
Jogging/running					
Aerobics					
Swimming					
Golf					
Dance					
Athletics					
Cricket					
Rugby					
Skateboarding					
Soccer					
Hockey					
Volleyball					
Surfing					
Basketball					
Gymnastic					
Squash					
Martial arts					
Other :(specify).....					

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

I do not do P.E	
Hardly ever	
Sometimes	
Quite often	
Always	

3. In the last 7 days, what did you do most of the time at first break? (check one only)

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

4. In the last 7 days, what did you normally at second break? (check one only)

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

5. In the last 7 seven days, on how many do sports, dance or play games in which you were very active?(check one only)

None	
1 time last week	
2 or 3 times last week	
4 times last week	
5 time last week	

6. In the last 7 days, on how many evenings did you do sports, dance or play games in which you were very active(tick only one)

None	
1 time last week	
2 or 3 times last week	
4 times last week	
5 times last week	

7. On the last weekend, how many times did you do sports, dance or play games in which you were very active?(tick only one)

None	
1 time	
2-3 times	
4-5 times	
6 or more times	

8. Which one of the following describes you best for the last 7 day? Read all five statements before deciding on the one answer that describes you.

A. All or most of my free time was spent doing things that involve little physical effort	
B. I sometimes (1-2 times last week) did physical things in my free time (e.g. played sports, went running, swimming, bike riding, did aerobics)	
C. I often (3-4 times last week) did physical things in my free time	
D. I quite often (5-6 times last week) did physical things in my free time	
E. I very often (7 or more times last week) did physical things in my free time	

9. Mark how often you did physical activity (like playing sports, games, dancing, or any other physical activity) for each day last week.

	None	Little bit	Medium	Often	Very often
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

CONSENT FORM FOR RESEARCH PARTICIPATION

Your child is invited to participate in a research study being conducted by the investigators listed below. Prior to participating in this study you are asked to read and sign this form, which outlines the purpose and gives a detailed description of the testing procedures used in this study. The testing procedures will be conducted at the school during school hours.

INVESTIGATORS	PHONE
---------------	-------

Mr X. Hlengwa

0846450156

Mr P. Msane

0843712332

PURPOSE

The Department of Biokinetics and Sport Science at the University of Zululand is currently conducting a research study in which we are investigating the Modification of Cardiometabolic Disease Risk Factors in Primary School Children. Cardiometabolic disease is a cluster of interrelated risk factors that promote the development of cardiovascular disease and type 2 diabetes. The specific factors that can cause this increased risk include: insulin resistance, hypertension, hyperglycemia, and dislipoproteinemia. Limited data exists on the association between physical activity and cardiometabolic risk in children. Therefore, identifying children at risk for the development of cardiometabolic risk is imperative for prevention and intervention.

OVERVIEW OF TESTING PROCEDURES

All testing procedures will occur at the school during school hours.

Physical measurements

Blood analysis

Intervention program

TESTING PROCEDURES

Physical measurements

These non-invasive measurements will include body mass index, waist-to-hip ratio, skinfold measurements, cardiorespiratory fitness, resting blood pressure, heart rate variability, and arterial stiffness.

Blood Analysis

A qualified nurse from LANCET laboratories will take blood from your child's arm. They will take a second sample after 10 weeks. The blood sample will be used to measure glucose, insulin and endothelial inflammatory markers (C-reactive protein, adiponectin, endothelial progenitor cells, e-selection, NO, vascular endothelial growth factor). These measurements are associated with cardiometabolic risk factors.

Intervention program

The 6-week physical activity intervention will be conducted 3-5 days per week during school hours for an hour. The physical activities will be age appropriate and enjoyable for your child.

WITHDRAWAL FROM STUDY

If you and your child first agree to participate and then you or your child changes his/her mind, you and your child are free to withdraw your consent and discontinue your child's participation at any time.

POSSIBLE RISKS AND DISCOMFORTS

Risk of blood draws

Drawing the blood may hurt a little. There is a risk of some bruising, bleeding, and slight soreness at the puncture site. Although most of the risks stated above are infrequent and/or resolve spontaneously.

CONFIDENTIALITY

Your child's identity will be kept as confidential as possible as required by law. In order to maintain confidentiality of your child's records, the investigators will make use of codes representing each participant.

BENEFITS

Your child will have the opportunity to improve his/her physical fitness level which is related to improved self-esteem. You will also receive a report outlining your child's results. Tests like the above can cost up to thousands to conduct, if your child participates in this research study, these tests will all be FREE and results will be made available to you! This could detect any worrisome areas before they become chronic/severe and potentially have a negative long term effect on your child, thus enabling you to enhance and better your child's quality of life. The information gained through this study will give you valuable information about your child's health and potentially help current generations as well as those generations to come.

QUESTIONS

Any questions concerning the research study or your child's participation in it, before or after your consent, will be answered by the main investigator Ms Anneke van Biljon, 0829057635, vanbiljona@unizulu.ac.za.

CONSENT FORM FOR PARTICIPATION

Consent Statement:

I, _____ (please print the name & surname of parent/guardian) understand the purpose and procedures of this research project as described and I voluntarily agree to allow my child, _____, to participate in the research project titled *Modification of Cardiometabolic Disease Risk Factors in Primary School Children*.

I have read the above information. The nature, demands, risks and benefits of the program have been explained to me. I knowingly assume the risks involved and understand that at any time during the research program we will be free to withdraw my consent and discontinue participation at any time without penalty or loss of benefit to myself.

Signature of Parent/Guardian Date

Signature of Child Date

I certify that I have explained to the above individual the nature and purpose, the potential benefits and possible risks associated with participation in this research study.

These elements of informed consent conform to the Assurance given by the University of Zululand to the Department of Health and Human Services to protect the rights of human subjects.

Signature of Investigator 26 January 2016
Date

UNIVERSITY OF ZULULAND
DEPARTMENT OF
SPORT SCIENCE & BIOKINETICS



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26 January 2016

RESEARCH PROJECT: Cardiometabolic Disease Risk Factors in Children

The Department of Biokinetics and Sport Science at the University of Zululand is currently conducting a research study in which we are investigating the *Modification of Cardiometabolic Disease Risk Factors in Primary School Children*.

Cardiometabolic disease is a cluster of interrelated risk factors that promote the development of cardiovascular disease and type 2 diabetes. The specific factors that can cause this increased risk include: obesity, insulin resistance, hypertension, hyperglycemia, and dislipoproteinemia. Limited data exists on the association between physical activity and cardiometabolic risk in children. Therefore, identifying children at risk for the development of cardiometabolic risk is imperative for prevention and intervention. In addition, whilst physical activity guidelines have been established it is not known which type of intervention is most effective in reducing cardiometabolic disease risk. That is, by manipulating the intensity and frequency of a physical activity intervention programme in overweight children can more pronounced health benefits be derived?

The aim of the study is to design, implement and compare the efficacy of three different intervention programmes on improving cardiometabolic health in sedentary primary school children.

An age appropriate physical activity intervention programme for children in grades 5 and 6 will be offered for 6-weeks during February and July 2016. The study will consist of four groups:

- Group 1 will participate in a low-moderate intensity physical activity programme which will entail three 40-minute sessions per week.
- Participants in group 2 will be allocated to a high intensity physical activity programme requiring three 40-minute sessions per week.

- Group 3 will participate in an alternate intensity physical activity programme for five 40-minute sessions per week.
- Group 4 will not participate in any intervention programme and will serve as the control group, continuing with their everyday activities. This is done to allow group comparisons.

Exercise intensity of the sessions will be measured both subjectively and objectively with a RPE-scale and heart rate monitor respectively.

Permission will be sought from the learners and their parents prior to their participation in the research. Only those who consent and whose parents consent will participate.

Once I have received your consent to approach learners to participate in the study, I will

- arrange for informed consent to be obtained from participants' parents
- arrange a time with your school for data collection to take place
- obtain informed consent from participants

The role of the school is voluntary and the School Principal may decide to withdraw the school's participation at any time. This study has met the requirements of the Research Ethics Committee.

I look forward to your help with a project that can make a difference.

Yours sincerely

Anneke van Biljon

Project Supervisor

Invoice number: 50761
Invoice date: Mon Jul 02, 2018
Order number: 334359



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For the attention of:

Anneke van Bijl
annekevanbijljongeel@gmail.com

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