

The Metabolic Syndrome
and the Effects of Different Types of Exercise Modalities in Adolescents with Obesity:
A HEARTY Study

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Faculty of Health Sciences, School of Human Kinetics University of Ottawa, Ottawa, Canada
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Abstract

Purpose: The metabolic syndrome (MetS) is a cluster of metabolic abnormalities including high waist circumference and blood pressure, elevated triglyceride, glucose, and, insulin concentrations and low high density lipoprotein cholesterol concentrations. The prevalence of MetS in overweight and obese adolescents ranges from 10 to 66% depending of the definition used and the population studied. Obese adolescents are more prone to have MetS, highlighting the necessity of designing effective none pharmacological interventions targeting the specific needs of adolescents and to improve the management of the metabolic syndrome. **Objectives:** The objectives of this thesis were first, to perform a secondary data analysis of the Healthy Eating Aerobic and Resistance Training in Youth (HEARTY) trial to determine the effects of different modalities of exercise training on the prevalence of the MetS and second, to do a critical analysis of the literature surrounding the MetS concept and diagnostic for the pediatric population. **Methods:** Among the 304 participants of the HEARTY trial, 65 (21%) participants were classified as having MetS by the International Diabetes Federation. Measures of waist circumference, blood pressure, fasting plasma concentrations of lipids, glucose and insulin and prevalence of MetS were compared to baseline and post-6 months intervention (Aerobic training, Resistance training, Combined aerobic and resistance training and Control). **Results:** There were no significant changes in the prevalence of MetS within and between Aerobic, Resistance, Combined aerobic and resistance and Control groups after the 6-month intervention. However, significant improvements in MetS parameters were observed from baseline to post-intervention within groups. Aerobic and Resistance training alone significantly decreased waist circumference and systolic and diastolic blood pressure. Combined aerobic and resistance significantly decreased triglyceride concentrations and increased high density lipoprotein cholesterol

concentrations whereas Control significantly decreased systolic blood pressure and insulin levels.

Conclusions: Exercise, regardless of the modality, and diet counseling were not statistically effective for reducing the prevalence of MetS but did improve some of the independent MetS parameters. The absence of statistical difference in the prevalence of the MetS may be due to a lack of statistical power. Moreover, the critical analysis of the MetS literature bring us to conclude that the first step towards a standard definition of MetS for the adolescent population is to define the true clinical purpose of a MetS diagnostic in the pediatric population.

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List of Abbreviations

Adult Treatment Panel III (ATP III)
Body Mass Index (BMI)
Cardiorespiratory fitness (CRF)
Cardiovascular Disease (CVD)
Follicle-stimulating hormone (FSH)
Free Fatty Acid (FFA)
Glucose transporter type 4 (GLUT4)
Growth Hormone (GH)
Gonadotropin-releasing hormone (GnRH)
Oral Glucose Tolerance Test
High Density Lipoprotein Cholesterol (HDL-C)
Insulin-like Growth Hormone Factor I (IGF-I)
International Diabetes Federation (IDF)
Low Density Lipoprotein Cholesterol (LDL-C)
Luteinizing hormone (LH)
Metabolic Syndrome (MetS)
National Health and Nutrition Examination Survey (NHANES)
National Center for Health Statistics (NCHS)
National Cholesterol Education Program (NCEP)
Oral Glucose Tolerance Test (OGTT)
Physical fitness (PF)
Percentage Body Fat (%BF)
Quantitative Insulin Sensitivity Check Index (QUICKI)
Type 2 Diabetes (T2D)
World Health Organization (WHO)

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CHAPTER I

INTRODUCTION

1.1 Background

Historically in times of famine, more adiposity was protective and a survival advantage against under-nourishment and infection. However, in the past few decades, obesity or excessive fatness has arguably become the primary childhood health concern in developed nations and progressively in other parts of the world. The increase in childhood obesity worldwide has gained much attention from researchers, healthcare professionals, health policy experts, educators, and parents. There is much concern that today's overweight and obese children and adolescents will become overweight and obese adults and will be confronted with co-morbidities associated with adulthood obesity.

1.2 Rationale and statement of the problem

There is a strong link between obesity and the metabolic syndrome (MetS) in adults.¹ MetS is a cluster of metabolic abnormalities (combination of abdominal obesity, insulin resistance, dyslipidemia and hypertension) associated with an increased risk of cardiovascular disease (CVD) and type 2 diabetes (T2D).² Considering the increased incidence and prevalence of childhood obesity³, it is not surprising that a sub-group of overweight or obese children have been identified to have the MetS, leading to fears regarding increasing risk of earlier onset of chronic disease such as T2D, CVD and mortality.¹ Therefore, efficient prevention and treatment strategies for obese adolescents identified with MetS are critical. The first line of treatment for MetS is often pharmacological, depending on which risk factor are elevated, although it may also include weight loss induced by a caloric restriction and/or increased exercise. Very little is known about the effects of different types of exercise interventions such as aerobic, resistance or combined training on prevention and treatment of the MetS. Therefore, there is a need to

examine the impact of different exercise modalities on the MetS in obese adolescents. Results could inform exercise program development for MetS reduction among adolescents.

1.3 Objectives

The primary objective of the Healthy Eating Aerobic and Resistance Training in Youth (HEARTY) randomized controlled trial was to evaluate the effects of aerobic training, resistance training, and combined aerobic and resistance training on percent body fat in inactive post-pubertal overweight or obese adolescents aged 14–18 years old.⁴ Subsequently, this thesis is a secondary analysis of the HEARTY 6-month trial. For the purpose of this thesis, two separate objectives were proposed and reported in two original manuscripts: 1) To compare the effects of aerobic training, with and without resistance training in adolescents with metabolic syndrome and; 2) to criticize the usefulness of a pediatric MetS definition.

1.4 Hypotheses

For article I, it was hypothesized that Aerobic and Resistance training alone would yield greater decreases in the prevalence of the metabolic syndrome than Control, and Combined training would show greater decreases than Aerobic or Resistance training alone.

Article II is a critique on the usefulness of diagnosing MetS among adolescents. An hypothesis was not applicable.

1.5 Relevance

This study will advance our understanding of using exercise as an intervention strategy to treat MetS in adolescents. As a whole, the results of this thesis will provide insight on the

preferred exercise modality for treating MetS and a better understanding of the effects of different exercise modalities on individual MetS parameters (abdominal obesity, blood pressure, blood lipids and fasting glucose) in adolescents with obesity. This newly acquired knowledge could be disseminated to primary care physicians, youth training centres and clinics to promote different exercise modalities as effective treatment options suited for younger obese populations with MetS. Future studies can build on our findings to examine the optimal duration and intensity of an exercise intervention to mitigate or reverse the complications of the MetS.

1.6 Delimitations and limitations

The participants recruited for the HEARTY study were physically inactive and overweight or obese adolescents aged 14 to 18 years. Therefore, the results of this study may not apply to lean and/or active children under the age of 14 years old (pre-pubescent children) or over the age of 18 years old (adults). Pre-pubertal and post-pubertal children differ significantly in pubertal maturation, growth and development and thus, in MetS parameters. Overall, results of this study will be limited to overweight and obese inactive adolescents.

CHAPTER II

REVIEW OF LITERATURE

2.1 Introduction to childhood obesity

2.1.1 Childhood obesity classification

Typically, overweight and obesity in the pediatric population are defined as a body-mass-index (BMI) above a particular percentile. BMI is defined as weight in kilograms divided by height in meters squared (kg/m^2). However, BMI has its limitations.⁵ Since children are growing, the link between adiposity and the ratio of their weight and height might be less fixed than in adults. Nevertheless, researchers have reported that BMI is a reasonable measure to assess fatness in children and adolescents.⁶ BMI percentile cutoff points that are categorized by age and sex are used to identify overweight and obesity in children and youth aged 2 to 18 years. A BMI above the 85th percentile for a child's age and sex group is likely in accordance with the adult definition of overweight, and above the 95th percentile with that of the adult definition of obesity.⁷ In 2007, the World Health Organization (WHO) proposed the WHO Reference 2007, which is a reconstruction of the 1977 National Center for Health Statistics (NCHS)/WHO reference.⁷ This reference presents growth reference data from children and adolescents. It uses the original NCHS data set and includes data from the WHO child growth standards sample for children under the age of five.⁷ Therefore, these new growth curves are used to derive BMI and classify childhood obesity.

2.1.2 Prevalence

In the past 20 years, childhood obesity has become a worldwide epidemic. Between 1980 and 2000, the prevalence of childhood obesity tripled in the United States and similar trends were also observed in the United Kingdom, China, Germany, France, and Finland.^{8,9} In Canada, the prevalence of overweight and obesity increased from 15% in 1979 to 31.5% according to the 2009 to 2011 Canadian Health Measures Survey.¹⁰ Nearly one-third of all Canadian children are

considered overweight or obese.¹⁰ It places millions of children at risk of developing poor mental health, and lower quality of life^{11,12} as well as chronic diseases such as T2D, dyslipidemia and CVD, among others (Table 1).¹³ It is now well established that children who are overweight at an early age are more prone to become overweight adolescents and obese adults.^{14–16} In fact, it has been shown that approximately 80% of obese adolescents become obese adults.¹⁷ Barker et al.¹⁸ showed that a rapid increase in BMI during preschool aged 2 to 11 years affects adulthood morbidity and predicts later coronary events in both men and women, emphasizing the importance of early intervention. Evidence suggests that long-term complications such as CVD and T2D associated with early onset of obesity can be anticipated. In a 32-year Dutch prospective study, a significant increase in mortality was observed in the adults who were overweight or obese as adolescents/young adults aged 18 years (defined as a BMI ≥ 25 kg/m²).¹⁹ Another Swedish study revealed that obese children showed a higher premature mortality rate in comparison with lean children at a 40 year follow-up²⁰ and that the most common cause of death was CVD.²⁰ The Harvard Growth Study followed Caucasian adolescents for 55 years and demonstrated an excess morbidity and mortality in those who were overweight in adolescence (13 to 18 years), even after adjusting for BMI at age 50.²¹ More specifically, the risk of morbidity from coronary heart disease in particular was increased among men and women who had been overweight in adolescence.²¹ In summary, the onset of overweight or obesity during adolescence is associated with an increased risk of adverse health problems that are more likely to persist into- or exert their health effects in adulthood.²² Adolescent obesity has been associated with increased overall risk of T2D, CVD, and mortality in adults²³ and stresses the importance of considering childhood and adolescent obesity as a major public health concern.

Table 1. Adverse Effects Associated with Childhood Obesity¹⁷

Metabolic	
	Type 2 diabetes mellitus
	Metabolic syndrome
Orthopedic	
	Slipped capital femoral epiphysis
	Blount's disease
Cardiovascular	
	Dyslipidemia
	Hypertension
	Left ventricular hypertrophy
	Atherosclerosis
Psychological	
	Depression
	Poor quality of life
Neurological	
	Pseudotumor cerebri
Hepatic	
	Nonalcoholic fatty liver disease
	Nonalcoholic steatohepatitis
Pulmonary	
	Obstructive sleep apnea
	Asthma (exacerbation)
Renal	
	Proteinuria

2.1.3 Energy Balance

The basic theoretical physiological explanation of weight gain is well understood. When energy intake exceeds energy expenditure, weight gain will result in the majority of individuals.²⁴ Although some genetic endocrine and neurological syndromes such as Prader Willi, Klenefeler's, Frohlich's, Lawrence Mood Biedl, Klein-Levin, and Mauriac syndromes can lead to childhood obesity, it has been estimated that less than five percent of obesity cases result from these syndromes.²⁵

Although positive energy balance is the cause of weight gain and, over the long term, leads to obesity, there are many factors that contribute to the pediatric obesity epidemic. Over the past several decades, a range of environmental changes may have affected children's energy balance. Changes in the food industry such as increases in the volume and accessibility of fast food restaurants, increased portion size of soft drinks and food and greater costs associated with healthier foods are only some factors among numerous others that have likely driven the obesity epidemic.²⁶⁻³⁰ There is also evidence that advertising from the fast food industry is affecting food preferences and choices, even in children as young as 2-years-old.²⁷

Moreover, changes in the built environment have led to increased sedentary behaviour and decreased physical activity among children and adults.^{17,31} Changes in childcare and in the school environment have been particularly notable. The availability of unhealthy foods and beverages available at school, as well as the decrease in physical education requirements promote an obesogenic environment.³² In sum, many environmental changes can promote increases in energy intake and decreases in energy expenditure among children and adolescents.

2.2 Adolescence: a critical period

“A critical period refers to a specific period of development when an insult has an

enduring effect on the structure or function of organs, tissues, and body systems. If not completely deterministic, these periods are often referred to as sensitive rather than critical.”¹⁷ Adolescence (13–19 years) is a transitional period characterized by dynamic physiological and psychosocial changes in both boys and girls.³³ Drastic changes in growth, body composition, insulin sensitivity, puberty, maturation, and fitness are driven by biological processes, with the onset of puberty marking the passage from childhood to adolescence. Evidently, adolescence is believed to be a critical period for the development and persistence of obesity and related co-morbidities into adulthood in both sexes.^{34–37}

Adolescence is also characterized by substantial increases in adipocyte (fat cell) size and number. Adipose tissue hypertrophy (increase in fat cell size) and hyperplasia (increase in the number of fat cells) are associated with intracellular abnormalities of adipocyte function by affecting the endoplasmic reticulum and posing mitochondrial stress.³⁸ These processes result in intracellular and systemic consequences including adipocyte insulin resistance, production of adipokines, free fatty acids, and inflammatory markers, as well as promotion of cardiometabolic abnormalities. Adipose tissue hypertrophy and hyperplasia increases the risk of obesity and clinical cardiometabolic abnormalities.³⁸

Other developmental changes, namely the quantity and location of body fat, differ between boys and girls during puberty. Boys tend to show an increase in fat-free mass and a decrease in total percent body fat (% BF) whereas in girls, both fat mass and fat-free mass increase but not proportionally, leading to an increase in total % BF during adolescence.³⁹ Moreover, body fat distribution patterns also differ by sex. Central adiposity, with increases in abdominal subcutaneous fat and especially visceral fat, occurs in boys; this pattern is similar but less pronounced in girls. For the latter, fat tends to be deposited subcutaneously in the breasts,

hips, and buttocks during this period.⁴⁰ From an evolutionary perspective, more body fat in females has been favourable for healthy pregnancy. Overall, during puberty, girls are at an increased risk of acquiring excess weight given a greater increase in adipocyte number and size in the subcutaneous gluteal (buttocks) region compared with boys of similar age during adolescence.^{41–43}

2.3 Pubertal maturation

2.3.1 Physiological changes that occur during puberty

The primary basis for physical growth during childhood is the growth hormone (GH)/insulin-like growth factor I (IGF-I) axis.⁴⁴ Growth hormone is a hormone synthesized and secreted by the anterior lobe of the pituitary gland that promotes growth and increases the synthesis of proteins essential for growth. The effects of GH are both anabolic and metabolic. GH stimulates epiphyseal and osteoblastic activity in bone and promotes lean tissue development (i.e., increased amino acid transport and nitrogen retention in muscle).⁴⁴ Moreover, GH has a lipolytic, insulin-resistant action.⁴⁵ To promote growth, GH and IGF-I exert a powerful influence on energy metabolism. The GH/IGF-I axis induces increases in growth velocity, bone and muscle maturation, functional ability and metabolic adaptation.

The beginning of puberty is characterized by an increase in gonadotropin-releasing hormone (GnRH) and in gonadotropin secretion through the hypothalamic–pituitary–gonadal axis.⁴⁶ This axis controls development, reproduction, and aging in animals. The hypothalamus produces GnRH. The anterior portion of the pituitary gland produces luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the gonads produce estrogen and testosterone. During early puberty, pulsatile gonadotropin secretion amplifies and mostly happens during

sleep, with relative quiescence during the day.⁴⁶ As puberty progresses, the amplification of pulsatile gonadotropin secretion gradually increases during the day. At the end of puberty, an adult pattern of gonadotropin secretion is established, which leads to the development of secondary sexual characteristics.⁴⁶ In girls, maturation of gonadotropin secretion promotes ovarian follicular development, estradiol production and ovulation.⁴⁶ Eventually, the gonadotropin-driven ovarian estrogen production promotes thelarche, the initial appearance of breast tissue.⁴⁶ Estrogen production also contributes to pubertal changes in body fat composition and distribution. In boys, maturation of gonadotropin secretion promotes gonadarche (testicular enlargement) and testosterone secretion.⁴⁶ Gonadarche is followed by progressive masculinization (scrotal development, penile length and width, male-pattern hair development, etc). Increased sex steroid production continues throughout puberty, translating into clinical signs of pubertal development (such as breast growth, menarche, enlargement of testicles, facial hair, etc). Physical changes associated with puberty are well-documented using clinical stages proposed by Marshall and Tanner.^{47,48} Clinical stages (1 = prepubertal to 5 = fully mature) are presented in Table 2.

Table 2. Tanner pubertal stages^{47,48}

Girls	
Stage I	Preadolescent; elevation of papilla only
Stage II	Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter
Stage III	Further enlargement of breast and areola, with no separation of their contours. (Note that menarche occurs mainly in stages 3 and 4.)
Stage IV	Projection of areola and papilla to form a secondary mound above the level of the breast
Stage V	Mature stage; projection of the papilla only, owing to recession of the areola to the general contour of the breast
Boys	
Stage I	Preadolescent; testes, scrotum and penis are of approximately the same size and proportion as in early childhood
Stage II	The scrotum and testes have enlarged, and there is a change in the texture of the scrotal skin. There is also some reddening of the scrotal skin.
Stage III	Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of testes and scrotum.
Stage IV	Penis further enlarged in length and breadth with development of glands. Testes and scrotum further enlarged. There is also further darkening of the scrotum skin.
Stage V	Genitalia adult in size and shape. No further enlargement takes place after stage 5 is reached.

2.3.2 Physiological changes during puberty in children and adolescents with obesity

Obesity, particularly beginning at a young age, may lead to accelerated growth. Obese pre-pubertal children are typically taller and have advanced bone ages than non-obese pre-pubertal children.^{49,50} Despite this rapid growth, obese children have low GH plasma concentrations because of reduced GH pulsatile release and increased GH clearance.⁵¹ In obese females, excess body fat has been associated with an early onset of puberty and early menarche.⁵² An American research group examined 17 000 girls from across the country and found that the onset of female puberty is occurring earlier than predicted by current norms.⁵³ Herman-Giddens and colleagues found a mean age for breast development of 8.9 years and 10.0 years in African-Americans and Caucasians respectively,⁵³ in comparison to 10.9 years based on the current average.⁵⁰ According to the results of this study, girls are heavier and taller than in the first and second National Health and Nutrition Examination Surveys (1971 and 1976-1980, respectively).⁵⁴ However these trends are related to the overall increase in weight of American children,⁵⁵ and they do not infer a causal relationship between excessive adiposity and early puberty.

In obese boys, the onset of puberty varies considerably. Obesity has been linked to both early maturation and pubertal delay in boys.^{56,57} Severe obesity may also delay the timing of pubertal maturation.^{56,58} Hence, considerable variability in pubertal progression is observed among obese males.^{53,59} Gynecomastia, a benign enlargement of breast tissue, is common among obese pubertal males. The breasts are often greater in size and more persistent over time compared to boys with a normal pubertal gynecomastia.⁶⁰

Interestingly, plasma leptin concentrations in both sexes have been proposed as a potential link between body weight, the onset of puberty and menarche. Leptin, is a hormone

produced by adipocytes that plays a key role in regulating energy intake and energy expenditure.⁶¹ Through its hypothalamic receptor, leptin provides a signal to the brain regarding the amount of body fat stores.⁶¹ It also regulates appetite and metabolism. Plasma leptin concentrations are strongly correlated with body weight and body fat mass.⁶² In normal weight males, an increase in leptin levels of approximately 50% has been observed before the onset of puberty.⁶³ In early puberty, plasma leptin concentrations typically increase in males and females,⁶⁴ although levels subsequently decline in males after puberty.⁶⁵ In females, plasma leptin concentration remains constant during mid-puberty, but rises in late puberty.⁶³ Moreover, there is an inverse relationship between plasma leptin concentration and age of menarche up to a certain level of leptin.⁶⁶ Leptin indirectly regulates gonadotropin-releasing hormone. Observations in rodents suggested that central pulsatile gonadotropin secretion is stimulated by the feedback from fat mass, which triggers the timing of puberty.^{67,68} Similar results in humans indicate that although leptin may play a role in puberty onset, it might not necessarily be the critical element in the timing of puberty. This was demonstrated in longitudinal studies whereby, there was gradual rise in leptin from the pre-puberty into early puberty but then a wide range in leptin levels at the onset of puberty, around the age of 11-12 years, rather than a single general threshold.^{65,69}

2.4 The Metabolic Syndrome

First introduced in 1988 as “Syndrome X”, then renamed Metabolic syndrome (MetS), is defined as a cluster of metabolic abnormalities (combination of abdominal obesity, insulin resistance, dyslipidemia and hypertension) associated with an increased risk of T2D and CVD, greater than associated with its individual components.² The MetS is also referred to in the

literature as “insulin resistance syndrome” because Reaven hypothesized that insulin resistance is the key component linking this cluster of metabolic abnormalities.² Epidemiological studies have demonstrated that the MetS is common in adults (between 20-40% depending on the definition used), especially among obese individuals, and that its incidence is increasing as the epidemics of obesity increases.^{70,71} Furthermore, there is growing evidence that, in adults, MetS significantly increases CVD morbidity and mortality.^{70,71} However, obesity and the MetS do not necessarily co-exist. In fact, not all overweight or obese individuals have the MetS or are considered ‘metabolically unhealthy’.⁷²

Since 1988, the concept of the MetS has become increasingly studied and additional diagnostic criteria have been proposed, such as the presence of microalbuminuria (abnormally high permeability for albumin in the renal glomerulus), indices of sub-chronic inflammation, endothelial dysfunction, alterations in the hemostatic system and non-alcoholic fatty liver disease.^{70,71} Hence, many definitions of MetS for adults have been proposed over the years, including those from the WHO, the Adult Treatment Panel III (ATP III), the European Group for the Study of Insulin Resistance, the American College of Endocrinology, the American Heart Association/National Heart, Lung and Blood Institute as well as the International Diabetes Federation (IDF).^{70,71,73} The main differences between the proposed definitions are the set of specific metabolic parameters taken into account and differences in threshold cutoffs for health risk.

2.4.1 Pathogenesis of the Metabolic Syndrome

The pathogenesis of the MetS is not yet fully understood. It is believed that obesity and insulin resistance are the two key players in the pathophysiology of the MetS.⁷¹ In both adults

and children, obesity is considered the main determinant of insulin resistance.⁷⁴ Interestingly, body fat distribution is recognized as an important predictor of the adverse health consequences of obesity. In fact, there is a growing body of evidence showing that abdominal visceral fat plays a more important role in the development of insulin resistance in both adults and children than overall body fatness.⁷⁵ Caprio et al. demonstrated that the amount of visceral fat was directly correlated with basal and glucose-stimulated insulin levels and inversely correlated with insulin sensitivity and the rate of glucose uptake.⁷⁵ Conversely, either no correlation or low correlations were observed between abdominal subcutaneous fat and the same metabolic indices.⁷⁶ Based on the ‘portal theory’, these findings could be related to a higher lipolytic activity of visceral fat adipocytes compared with subcutaneous fat cells, resulting in a higher turnover rate of free fatty acids (FFA) and glycerol delivered directly to the liver.^{71,77}

Ectopic deposition of fat in the liver or muscle can also lead to insulin resistance in obese individuals.⁷⁸ In muscle, increased plasma FFA disrupts the glucose-fatty acid cycle and has an inhibitory effect of elevated plasma FFA on insulin-mediated glucose transport.⁷¹ Moreover, increased FFA plasma levels have been shown to impair hepatic insulin action, increase hepatic glucose output and increase the synthesis of proinflammatory cytokines as well as alter lipoprotein metabolism.⁷¹ The accumulation of fat depots in liver and muscles impairs insulin signaling, with reduced glucose uptake in the muscle and decreased insulin-mediated suppression of hepatic glucose production.⁷⁸ In addition, intramyocellular lipid accumulation is also associated with insulin resistance.^{79,80} In children, Weiss et al.⁷⁸ demonstrated that ‘obese insulin-resistant’ children and adolescents are characterized by higher levels of visceral fat and intramyocellular lipid compared with ‘obese insulin-sensitive’ peers, despite similar degrees of adiposity.

In addition to abdominal visceral obesity and insulin resistance, other factors have been identified as potential contributors to the pathophysiology of the MetS: maternal obesity, gestational diabetes, ethnicity, birth weight, family history of diabetes, as well as genetic factors.⁷¹ Additional factors that may also play a role in the pathophysiology of the MetS are the immune system, chronic stress and dysregulation of the hypothalamic-pituitary- adrenal axis, autonomic nervous system, increases in cellular oxidative stress, renin-angiotensin-aldosterone system activity, and intrinsic tissue glucocorticoid actions.⁷¹

2.4.2 The Metabolic Syndrome in Children

The MetS has been well-documented in adults and has been linked to CVD morbidity and mortality.⁸¹ Considering the increase in the incidence and prevalence of childhood obesity³ and the strong link between obesity and MetS,¹ it is not surprising that the MetS has been identified in a sub-group of overweight or obese youth, leading to fears of earlier onset of chronic disease such as T2D, CVD and premature mortality.¹

2.4.3 Attempt to define the Metabolic Syndrome

Adult definitions were initially applied to the pediatric population.⁸² The use of adult definitions was hampered by several problems. Specifically, the featured cut offs for MetS must be age- and sex-specific due to the age- and sex-dependent variation in anthropometric parameters (BMI and waist circumference) as well as metabolic and cardiovascular parameters (lipids and blood pressure). Therefore, many scientific groups have proposed different definitions of MetS for pediatric populations (Table 3). However, there is a lack of consensus among MetS definitions that is partly due to our evolving understanding of normal physiologic and metabolic development that occurs during childhood and puberty. This has led to the

Table 3. Different Criteria Proposed by Different Authors for Diagnosing Metabolic Syndrome in Children

Criteria	Cook et al. ⁸³	De Ferranti et al. ⁸⁵	Cruz et al. ⁸⁶	Weiss et al. ¹	Ford et al. ⁸⁷
Central adiposity	WC $\geq$ 90th percentile (age and sex specific)	WC $>$ 75th percentile	WC $\geq$ 90th percentile (age, race and sex specific)	BMI – Z score $>$ 2.0 (age and sex specific)	WC $\geq$ 90th percentile (age and sex specific)
Triglycerides	$\geq$ 110 mg/dL (age and sex specific)	$\geq$ 1.1 mmol/L ($\geq$ 100 mg/dL)	$\geq$ 90th percentile (age and sex specific)	$\geq$ 95th percentile (age, race and sex specific)	$\geq$ 110 mg/dL (age specific)
HDL-C	$\leq$ 40 mg/dL (all ages/sexes)	$<$ 1.3 mmol/L ($<$ 50mg/dl)	$<$ 10th percentile (age and sex specific)	$<$ 5th percentile (age, race and sex specific)	$\leq$ 40 mg/dL (all ages/sexes)
Blood pressure	$\geq$ 90th percentile (age, sex and height specific)	$>$ 90th percentile	$>$ 90th percentile (age, sex and height specific)	$>$ 95th percentile (age, sex and height specific,	$\geq$ 90th percentile (age, sex and height specific,
Fasting plasma glucose	$\geq$ 110 mg/dL	$\geq$ 6.1 mmol/L ($\geq$ 110 mg/dL)	ADA criterion	ADA criterion	$\geq$ 110 mg/ dL (additional analysis with $\geq$ 100 mg/dL)
Diagnosis	$\geq$ 3 components	$\geq$ 3 components	$\geq$ 3 components	$\geq$ 3 components	$\geq$ 3 components

Note: WC, waist circumference; C, concentration; HDL, high density lipoprotein; BMI, body mass index

absence of specific cutoff values for certain parameters of the MetS and variations associated with different pubertal stages and ethnic groups that are not taken into consideration.

The first attempt to develop a pediatric definition of the MetS was in 2003 when Cook et al. adapted the NCEP/ATP-III criteria to a large population of American adolescents (n=2430) aged 12-19 years.⁸³ The definition included waist circumference over the 90th percentile, blood pressure above the specific age and sex 90th percentiles, while glycemia (≥ 110 mg/dl), triglycerides (≥ 150 mg/dl) and high density lipoprotein cholesterol (HDL-C) (< 40 mg/dl) had cut offs with absolute values.⁸³ The prevalence of MetS was significantly higher when the evaluation was restricted to obese adolescents compared to the whole population (28.7% vs. 4.2% respectively).⁸³ In 2004, Weiss et al.¹ investigated the association between the degree of adiposity and the increasing prevalence of the MetS in American youth aged 8-13 years. Alarming, the prevalence increased from 38.7% in moderately obese to 49.7% in severely obese youth.¹ In addition, there was a direct association between higher degree of insulin resistance and prevalence of the MetS, as previously demonstrated in an adult population.¹ Furthermore, data analysis from the National Health and Nutrition Examination Survey (NHANES) (1988-1994) and NHANES 1999-2000 revealed that the prevalence of MetS in children increased significantly from 4.2% to 6.4% in approximately 10 years.⁸⁴ The same year (2004), De Ferranti et al.⁸⁵ and Cruz et al.⁸⁶ proposed their own definitions of MetS. De Ferranti et al.⁸⁵ proposed a definition closely analogous to ATP III. The researchers observed that MetS is common in youth and that it had a similar ethnic distribution as adults in the NHANES (1988-1994).⁸⁵ They used an absolute cutoff value for HDL-C, triglycerides and fasting plasma glucose concentrations rather than cutoffs based on percentiles.⁸⁵ However, Cruz et al.⁸⁶ evaluated the relationship between directly measured insulin sensitivity and criteria of the MetS in overweight

Hispanic youth. They proposed a similar definition to ATP III but emphasized that age and sex must be taken into consideration, based on percentiles, for all MetS parameters.⁸⁶ In 2005, Ford et al.⁸⁷ investigated the relationship between chronic low-graded inflammation and the MetS among US adolescents (NHANES: 1999-2000). Based on their findings, Ford et al.⁸⁷ slightly modified the pediatric definition of MetS proposed by Cook et al. by lowering the fasting plasma glucose cutoffs from ≥ 110 mg/dl to ≥ 100 mg/dl.

2.4.4 International Diabetes Federation's attempt to unification

The International Diabetes Federation (IDF) tried to integrate the criteria from different organizations to unify the diagnosis of MetS in children and adolescents (Table 4). Authors grouped children into 3 age categories: 6 to <10, 10-16, and >16 years. This was particularly important because no specific criteria were proposed for children under the age of 10. For adolescents aged between 10 and 16 years, the primary criterion is waist circumference above the 90th percentile, while the other metabolic abnormalities were specific absolute cutoff values. Finally, the IDF decided that adult criteria would be used to identify the MetS in adolescents >16 years.

However, the specific pediatric definition proposed by the IDF has its limitations. In particular, three questions need to be considered: (1) Can MetS be diagnosed in pre-pubertal children (under the age of 10 years)? (2) Is waist circumference an easy and reliable adiposity measurement in the pediatric population? (3) Are there other important parameters that should be included in the definition of MetS for children and adolescents?

Table 4. Different Criteria Used by Organization for Diagnosing the Metabolic Syndrome in Children

Criteria	WHO	IDF (aged 10 to < 16 years)	NCEP
Central adiposity measured by WC	> 95 th percentile for age and sex	90 th percentile of WC or adult cutoff if lower	Waist ≥ 102cm (M) or ≥ 88cm (F)
Triglycerides	< 10 years of age: > 105 mg/dL (> 1.2 mmol/L) > 10 years of age: > 136 mg/dL (> 1.5 mmol/L)	≥ 150 mg/dl (> 1.7 mmol/L)	≥ 150 mg/dl
HDL-C	< 35 mg/dL (< 0.9 mmol/L)	< 40 mg/dl (< 1.03 mmol/L)	< 40mg/dl (M) or < 50 mg/dl (F)
Total cholesterol	> 95th percentile	-	-
Systolic blood pressure	> 95 th percentile for age and sex	≥ 130 mmHg	≥ 130 mmHg
Diastolic blood pressure	> 95 th percentile for age and sex	≥ 85 mmHg	≥ 85 mmHg
Fasting plasma glucose	Abnormal glucose homeostasis, such as fasting hyperinsulinemia, impaired fasting glucose, and impaired glucose tolerance (≥ 110 mg/dl)	≥ 100 mg/dl or T2D (> 5.6 mmol/L)	≥ 110 mg/dl or treatment for T2D
Diagnosis	Insulin resistance + ≥ 2 components	Central adiposity plus at least 2 of other components	≥ 3 components

Note: WHO, World Health Organization; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program; WC, Waist Circumference; T2D, Type 2 Diabetes M, Males; F, Females; HDL-C, High Density Lipoprotein-Cholesterol.

The first limitation is that no specific diagnostic criteria of the MetS have yet been proposed for children under the age of 10 years. This stands in contrast to an emerging body of evidence showing that many metabolic and cardiovascular abnormalities (e.g. liver steatosis, hypertension, diabetes, etc) are already present in pre-pubertal children with obesity.^{88–90} To our knowledge, there is no scientific evidence indicating that the MetS cannot be detected in children less than 10 years old.

The second limitation with the IDF pertains to waist circumference as the primary criteria for the diagnostic of the MetS. In this case, BMI is not used since it is a crude marker of adiposity and the degree of obesity per se is not a sufficient marker of metabolic dysregulation. Central adiposity correlates more strongly with waist circumference than BMI and is associated with metabolic and cardiovascular dysregulation.⁹¹ In spite of this, reference values of waist circumference exist only for some pediatric populations (e.g.: United States, United Kingdom, Canada, etc), limiting the use of the IDF criteria to multiple ethnic populations. More importantly, there is no standard measurement protocol to assess waist circumference in children and adolescents. A recent study compared four commonly recommended waist circumference measurement sites (iliac crest; narrowest waist between the xyphoid process and iliac crest; midpoint between the floating rib and iliac crest; and level of umbilicus) and demonstrated that different sites are not associated to the same degree with cardiometabolic risk factors.⁹²

Finally, other factors such as inflammatory markers, nonalcoholic fatty liver and obstructive sleep apnea are not currently part of the IDF criteria but may provide valuable information for identifying children and adolescents at risk for MetS.^{93–95} Arguably, measurement of some of these factors may not be feasible in a clinical setting. Overall, the IDF

definition has some limitations and further research is warranted to truly identify children and adolescents who are ‘at risk’ of MetS.

2.4.5 Concerns and limitations

The numerous definitions of the MetS in children and adolescents calls into question the true prevalence, incidence and tracking of this clinical diagnosis during childhood and adolescence.^{96,97} Interestingly, Goodman et al.⁹⁶ followed a cohort of 1098 teenagers over a 3-year period and found that the diagnosis of MetS based on the cutoff-point definitions was unstable over time. Up to half of the children with MetS at baseline did not meet the MetS criteria at follow-up, despite consistent risk factor clustering and deterioration of their metabolic profile.⁹⁶ Goodman et al.⁹⁶ suggested that due to MetS measurement variability or normal physiological growth and puberty, the clinical utility of MetS identification is questionable. Moreover, Gutstafson et al.⁹⁷ found that among obese children and adolescents aged 6 to 17 years, the diagnosis of MetS among 220 children was unstable in 31.6% of cases. In the long term, the diagnosis of MetS was unstable in 45.5% of cases.

From a statistical point of view, the majority of research on the criteria of the MetS was based on exploratory factor analysis although confirmatory factor analysis would be more appropriate.⁹⁸ Confirmatory factor analysis is a theory-driven approach, is more flexible and it allows individual factors to be correlated with each other in a manner specified by the investigator.⁹⁸ True physiological responses are more likely to be represented by correlations between some factors and not others.⁹⁸

Another limitation of the pediatric MetS definitions is the use of dichotomous ‘normal-abnormal’ variable categorization. The lack of specific normative values for all the MetS criteria

makes it difficult to describe the syndrome in a clear, unbiased way that is supported by underlying pathophysiological mechanisms. As mentioned, the well-known fluctuations associated with growth and puberty complicate the use of strict biological cut points. Instead of dichotomous variables, some investigators have suggested the use of a continuous risk score to improve the clinical utility of MetS diagnosis in children and adolescents. Despite these concerns, there is consistent indication that the prevalence of the MetS in children and adolescents has increased over the past few years. There is an urge to develop better screening tools and preventive and management programs to address this important public health problem.

2.5 Prevalence of the Metabolic Syndrome

It is difficult to determine the true prevalence of MetS in children and adolescents since there is no international standard definition for MetS in children and adolescents. Nonetheless, a recent systematic review analyzed 85 articles published since 2003 and found a median prevalence of the MetS of 3.3% (range 0%–19.2%) in the whole pediatric population, 11.9% (range 2.8%–29.3%) in overweight children, and 29.2% (range 10%–66%) in obese pediatric populations.⁹⁹

In Europe, the prevalence of the MetS was assessed in an Italian cohort of obese children aged 6-16 years (n=588) using WHO-derived criteria.¹⁰⁰ The prevalence increased across BMI tertiles (16% vs 23% vs 31%), supporting previous observations.¹⁰⁰ Notably, the frequency of the MetS gradually increased from Tanner stage I to stage IV and declined at stage V, regardless of sex.¹⁰⁰

It has been shown that the prevalence of MetS varies according to the definition used, the ethnicity, gender and age of the studied population.⁹⁹ Lee et al. applied five definitions to the

same population (129 Caucasians/122 African Americans, aged 8-19 years old)¹⁰¹ to identify prevalence of MetS in the United States. The authors found significant variability in MetS prevalence by definition used such that, the prevalence of the MetS were 13.4%, 18.7%, 21% and 25.1% using Cruz's, Weiss's, Cook's and Ford's criteria respectively.¹⁰¹ Similarly, Reinehr et al.¹⁰² applied eight proposed definitions of the MetS with a sample of 1205 Caucasian overweight and obese children and adolescents aged 4 to 16 years in Germany. Interestingly, the prevalence varied between 6% and 39% yet only 2% of youth fulfilled the criteria of the MetS across all definitions.¹⁰²

2.5.1 Effect of age, sex and ethnicity

The prevalence of MetS varies across age and sex and is generally higher in boys compared to girls.⁹⁹ This trend is also observed in adults, although sex differences may be less prevalent in adults.¹⁰³ Moreover, the prevalence of the MetS increases with age in adults and this holds true in children as well, as the incidence of MetS increases from childhood to adolescence.⁹⁹ However, one study found that the relationship between age and MetS was only seen in boys and not in girls.¹⁰²

Friend et al.⁹⁹ suggested that the prevalence of the MetS varies with ethnicity. A systematic review found that the Americas and Middle East might have a higher prevalence of MetS compared to Europe and the Far East (including India, South Korea and China).⁹⁹ Other studies, which applied the same MetS criteria to different nations (Brazil vs. Italy and United States Vs. Korea), support this observation.^{104–106} Nonetheless, researchers could not isolate a pattern for a higher prevalence of MetS in a specific ethnic group perhaps because different definitions were used to estimate its prevalence.⁹⁹

2.6 Effects of puberty and growth on Metabolic Syndrome parameters

As mentioned, puberty is characterized by many physiological changes, which may affect some of the parameters of the MetS. Differences in sexual maturation are apparent during puberty, which can affect body composition, hormone regulation, growth, etc.^{51,107} Those differences emphasize the importance of using percentile cutoffs (age and sex-specific) rather than absolute cutoffs during puberty until sexual maturity is reached.¹⁰⁸

2.6.1 Insulin sensitivity

Puberty presents a unique physiological challenge for the understanding of insulin-glucose homeostasis. Puberty is associated with marked changes in insulin action, insulin sensitivity and secretion, in both non-diabetic and diabetic children.¹⁰⁹ In a cross sectional study comparing insulin-stimulated glucose uptake, measured at two physiological concentrations of hyperinsulinaemia (80 and 480 pmol/l) between pre-pubertal adolescents, pubertal adolescents and adults, insulin-stimulated glucose uptake was reduced by 20% and 45% in lean adolescents compared with lean pre-pubertal adolescents and lean adults respectively.⁷⁵ The authors reported that during pubertal development, the deficits in insulin action involve pathways of non-oxidative glucose metabolism only.⁷⁵

Pubertal growth is associated with increases in plasma levels of GH, which increases rates of lipolysis in the liver, elevates circulating FFA and decreases insulin sensitivity.¹¹⁰ Lipolysis is the breakdown of triglycerides into FFA and it is sensitive to insulin.^{111,112} Still, another study investigated the effect of puberty on rates of lipolysis and found that the sensitivity of lipolysis to insulin is normal during puberty.¹¹³ Although tissue sensitivity to insulin declines during puberty, normal glucose homeostasis is maintained. Furthermore, Caprio et al.⁴⁵ sought to

establish the impact of insulin resistance on insulin secretion rates in pre-adolescents, adolescents and young adults using the hyperglycaemic clamp technique and they demonstrated a two- to threefold greater insulin response to glucose in adolescents compared with pre-adolescent children and adults.

During puberty, insulin resistance is normally compensated by increased insulin secretion.^{114,45,115} Studies have demonstrated a ~30% decrease in insulin sensitivity during puberty for boys and girls,^{110,116,117} regardless of adiposity levels.¹¹⁶ Although many hypotheses have been suggested to explain the decrease in insulin sensitivity during puberty, the precise mechanisms have not yet been established.¹¹⁸ Growth hormone has been proposed as one key factor involved in metabolic changes during puberty. Growth hormone has anti-insulin effects and common clinical manifestations of GH disorders include abnormalities of carbohydrate metabolism and insulin secretion.^{119,120} Thus, it has been proposed that GH hypersecretion accounts for the puberty-associated insulin resistance and, in turn, the increased β -cell response to glucose.

2.6.2 Blood pressure

Resting blood pressure increases over the transition between childhood and adolescence. Blood pressure is mainly influenced by stature or height, body composition and sex hormones. In the National Heart, Lung and Blood Institute growth and Health Study, 1213 African American girls and 1166 Caucasian girls aged 9 to 10 were recruited to investigate the effects of sexual maturation and racial differences on blood pressure.¹²¹ Authors reported that sexual maturation is an important correlate of blood pressure. Yet, results indicated that sexual maturation was associated with blood pressure independently of body size. In girls, systolic blood pressure rises

with pubertal stage independent of age.^{122,123,124} Overall, blood pressure seems to shift with height more closely than chronological age during pubertal stages, increasing two to four times faster than in the pre-pubertal growth period in girls.¹²⁵ In males, systolic blood pressure increased three to six times faster during pubertal growth than during the pre-pubertal growth period.¹²⁵ In both sexes, the changes in diastolic blood pressure during pubertal growth are much less pronounced than changes in systolic blood pressure but showed more variation with race.¹²⁵ Therefore, it is important to keep in mind that puberty impacts blood pressure.

2.6.3 Blood lipids

Plasma lipid concentrations vary during puberty.^{126,121,128} Total cholesterol usually decreases in mid-puberty and begins to rise toward adult levels near the end of puberty.^{128,76} These physiological changes in lipids complicate the diagnosis of dyslipidemia in youth, making it difficult to define specific lipid and lipoprotein cutoffs.¹²⁹ In addition, the decrease in physical activity and changes in eating habits that are commonly seen during adolescence may influence changes in body fat, blood pressure and lipid profiles during puberty.^{130,131}

In summary, MetS parameters may be dependent on pubertal maturation and associated with normal physiological changes that occur from childhood to adolescence. Many studies do not report the pubertal stages of their studied populations. Two children of the same chronological age can vary considerably with regard to sexual maturity. These differences emphasize the importance of including pubertal stages of the studied population to allow for more accurate comparisons.

2.7 Long-term Consequences of the Metabolic Syndrome

The need to track the prevalence of MetS risk parameters in longitudinal studies from childhood to adulthood is important to understand short and long-term effects on overall morbidity and mortality. Although the current literature in the pediatric population is limited, some longitudinal studies have been conducted. From the Muscatine Study Cohort data, Burns et al.¹³² reported that a BMI above the 75th percentile was significantly associated with a greater risk of developing MetS. They have shown that childhood BMI is the strongest predictor of MetS in adulthood.¹³² Also, adults with MetS had higher mean BMI, blood pressure and triglycerides during childhood.¹³² In addition, high BMI and high triglycerides during childhood increased risks of MetS more so than just high BMI in childhood.¹³²

Another prospective study evaluated the association between MetS during childhood and adult MetS and T2D.¹³³ Data showed that children diagnosed with pediatric MetS between the ages of 5 to 19 were 11.5 times (95% CI: 2.1-63.7, $p < 0.005$) more likely than their peers to have T2D 25 to 30 years later.¹³³ The presence of MetS during childhood (OD: 9.4) and a family history of diabetes (OD: 2.4) could increase children's risk of developing the MetS during adulthood.¹³³ Some researchers have suggested that having both factors may have a synergistic effect.¹³³

Further support for the link between childhood and adulthood MetS comes from two large longitudinal studies (Bogalusa Heart Study and Cardiovascular Risk in Young Finns Study).¹³⁴ Findings indicated that youth aged 9 to 18 years with the MetS had a two- to three-fold increased risk of having MetS during adulthood as well as increased intima media thickness and T2D compared with those without MetS during adolescence.¹³⁴ Interestingly, high BMI during childhood predicted each outcome as well as or better than the categorical MetS definitions that

were employed in this study.¹³⁴ In other words, youth with MetS are at increased risk of developing health-related issues in adulthood; however, screening for high BMI in the pediatric settings may be equally as accurate and simpler than the use of youth MetS definitions to predict adult MetS (and high intima media thickness and T2D) in adulthood.

The Princeton Follow-up Study, the Muscatine Study and the Fels Longitudinal Study also provide additional information on predicting MetS during childhood.¹³⁵ The three studies emphasized the predictive value of MetS in children and adolescents on future adult cardiometabolic risk factors.¹³⁵ Thus, it suggests that these MetS metabolic components may provide a useful screening approach to identifying children at risk.¹³⁵ Then, additional attention can be paid to children and youth who are more at risk of cardiometabolic complications and who may be in need of prevention and management interventions.¹³⁵

2.8. Treatment of the Metabolic Syndrome During Childhood and Adolescence

At the present time, there is no specific treatment for the MetS. Fundamentally, the etiology of childhood obesity, as with adulthood obesity, is the result of an energy imbalance (caloric intake in excess of energy expenditure), thus creating a positive energy balance. Intervention strategies to date target either side of the energy balance equation. Many influential factors have been reported in the literature as having an impact on energy balance, such as genetic, environmental, social-cultural, and family characteristics. Most of the daily energy expenditure is dictated by physical activity and resting metabolic rate and these key factors are obvious targets for interventions.

Physical activity refers to any bodily movement produced by skeletal muscles that results in energy expenditure above the basal metabolic level. Although exercise and physical activity are often used interchangeably in wider media, it is important to recognize established differences between the two.^{136–138} Exercise is considered a subcategory of physical activity and exercise or exercise training is, by definition, physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is the objective.^{136–138}

For treatment and prevention of obesity, health care providers and allied health professionals aim to provoke energy deficits to subsequently induce weight loss. Hence, interventions that aim at increasing physical activity and/or reduce sedentary behaviours are of particular interest to counter the increasing burden of obesity and co-morbidities in youth. Since the underlying mechanism of the MetS is thought to be obesity and insulin resistance, treatment strategies should focus on reducing the degree of adiposity, the associated insulin resistance early in life and treating individual components of the syndrome.¹³⁹ Interestingly, insulin sensitivity and the cardiometabolic profile of obese youth can be improved with lifestyle interventions, even in the absence of weight loss.¹⁴⁰ Therefore, lifestyle changes including a balanced diet appropriate for age, together with regular physical activity should be the core components of MetS treatment.¹³⁹ From this perspective, physical activity appears to be one of the most adaptive prevention and treatment options, and a number of physiological explanations have been put forward as to why physical activity may positively impact MetS and its components.^{314,117}

Of particular interest, prescribed exercise seems to be the preferred approach for physical activity interventions. In both adults and youth, exercising on a regular basis is associated with

many health benefits and it is proven to have an impact on the MetS parameters.^{142,143} According to the American College of Sport Medicine, prescribed exercise focuses mainly on cardiorespiratory and musculoskeletal fitness.¹⁴⁴ Cardiorespiratory exercise, generally referred to as aerobic exercise, is an activity performed at an intensity that allows the metabolism of stored energy to mainly occur through the use of oxygen. On the other hand, strength or resistance training, is a specialized method of conditioning musculoskeletal fitness that involves the progressive use of a wide range of resistive loads, including body mass, and a variety of training modalities. For the purpose of this paper, the term ‘aerobic’ and ‘resistance’ exercise training will be used to describe cardiorespiratory and musculoskeletal exercises respectively.

2.8.1. Evidence-based relationship between physical activity and Metabolic Syndrome clustering

Low levels of physical activity are associated with a high prevalence of MetS.¹⁴⁵ In fact, six studies conducted in healthy children using accelerometers as an objective tool to measure physical activity level found an inverse relationship between physical activity levels and the prevalence of metabolic risk factors independent of age, gender, BMI and adiposity.^{146–151} Furthermore, in overweight children, high cardiorespiratory fitness (CRF) was associated with a risk of presenting a MetS profile similar to that of normal-weight children with a low CRF.^{152–156} In other words, it eliminates the difference in prevalence rates of MetS reported between body weight classes: high CRF is protective of MetS regardless of body weight in children and adolescents. Cardiorespiratory fitness is associated with long-term prevention of metabolic abnormalities.¹⁵⁷ Over a seven-year follow-up, McMurray et al.¹⁵⁴ found, that high CRF was associated with a lower risk of MetS among children. Across studies, higher physical activity

levels are consistently associated with a more favourable metabolic profile and a reduced risk for MetS and/or insulin resistance in the pediatric populations.¹⁴⁵ Overall, many exercise intervention studies have found a negative relationship between physical activity and MetS parameters despite a wide range of participants, sample sizes, and exercise programs that differed in intensity, duration, modality and setting. A systematic review suggested that the impact of physical activity on the MetS appeared to be either independent of other factors, or alternatively, simultaneously mediated by the physical fitness and adiposity of the participants.¹⁴⁵ In fact, a dose-response relationship between MetS components and physical activity has been noted, meaning that greater improvements can be observed from interventions using a higher exercise volume and a longer duration.¹⁴¹ A recent systematic review by Janssen et al.¹⁴¹ concluded that youth engaged in physical activity programs showed health benefits, including improvements of MetS components. Data suggested that moderate and vigorous physical activity, but not low intensity physical activity, are associated with many health benefits including reduced risks of high blood cholesterol, high blood pressure, MetS, obesity, low bone density, depression, and injuries.¹⁴¹ Janssen et al.¹⁴¹ concluded that physical activity should mainly focus on aerobic activities with modest resistance training (2 or 3 days/week) for improvement of MetS components. The question of whether vigorous physical activity provides benefits beyond that of moderate physical activity, remains unanswered.

2.8.2 Impact of physical activity on insulin sensitivity

A relationship between physical activity levels and insulin sensitivity has been clearly established. Exercise increases insulin sensitivity both acutely and chronically.¹⁵⁸ Acute exercise is characterized by changes in insulin signaling in response to muscle contraction. There is an

increased translocation of glucose transporter type 4 (GLUT4) to the cell surface.^{159–162} GLUT4 are found in adipose tissues and striated muscle and are responsible for insulin-related glucose uptake and storage. Exercise increases GLUT4 content, glycogen synthase activity, mitochondrial enzyme activity and density in skeletal muscle^{157,160,163}. These are the underlying mechanisms to explain the relationship between physical activity and insulin sensitivity^{157,164} and for the proposed use of physical activity to decrease insulin resistance.¹⁶⁵ The acute effect can last up to 48 hours, which provides a rationale for recommendations to exercise regularly.

Physical fitness is a stronger predictor of insulin sensitivity than fatness in overweight children.¹⁶⁴ In addition, exercise improves insulin sensitivity via its improvement of body composition over the long term. Exercise also improves endothelial function and alters muscle fiber types.^{157,160,163} Long-term changes in insulin sensitivity within the skeletal muscle through regular exercise may improve whole-body insulin sensitivity.¹⁶³ The type, duration, frequency and intensity of physical activity can impact fuel metabolism during exercise (i.e., carbohydrate, fat and/or protein oxidation).¹⁶⁶

2.9 Impact of exercise on each parameter of the Metabolic Syndrome

The next section focuses strictly on the influence of exercise on MetS parameters without energy restriction and/or caloric deficit among adolescents aged 12 to 18 years. The objective is to tease out the effect of aerobic and/or resistance training on the parameters of MetS: waist circumference, insulin resistance, blood pressure and blood lipids. The goal is to demonstrate the value of exercise as an intervention tool. Although it is important to understand both sides of the energy balance scale independently, most intervention studies incorporate a combination of both diet and physical activity. Very few studies have focused solely on the effects of exercise and

examined only some of the MetS parameters. Studies that incorporated a nutrition component were not included and only exercise interventions will be discussed here.

2.9.1 Waist circumference

Obese adolescents enrolled in aerobic exercise training trials without dietary caloric restriction have shown changes in waist circumference from +1.4 to -6.1 cm.^{167–176} It is difficult to isolate the commonalities among studies showing favourable results because of the differences in exercise prescription. One research group from the Children’s Hospital of Pittsburgh recruited boys¹⁷² and girls¹⁷³ aged 12 to 18 years for a 3-months exercise trial. The aerobic intervention (treadmill, elliptical, or stationary cycling) was the same for both sexes and consisted of three exercise sessions per week for 40 to 60 minutes at 60%–75% of peak oxygen consumption ($VO_{2\text{ peak}}$). Similar waist circumference reductions were observed in boys and girls, although girls decreased (-2.5 cm) slightly more than boys (-2.0 cm).^{172,173} These results are encouraging since both sexes seem to respond similarly to the intervention. Similarly, Lee et al.(2010)¹⁷¹ reported a significant reduction in waist circumference (-6.1 cm) in 13 girls after a 12-week rope skipping intervention. This reduction can be deemed clinically important, especially given that waist circumference is the main criteria for the IDF MetS definition. The study by Lee et al.(2010)¹⁷¹ had a higher frequency (4 sessions per week) and intensity (80% of HR_{max}) than other studies suggesting that exercising more often at a higher intensity may yield greater improvements. In general, most studies provide evidence that engaging in regular aerobic types of exercise is associated with a moderate reduction in waist circumference and that it has a protective effect on age-associated increases in visceral fat in growing adolescents. From the evidence presented in Table 5, aerobic exercise training interventions at moderate to vigorous intensity (55% to 80%

Table 5. Effect of Aerobic training alone on Waist Circumference

Reference	Subjects	Age (yr)	Treatment	BMI (kg·m ⁻²)	Duration	Protocol	Exercise intensity	Δ WC (cm)
Randomized controlled trials								
Barbeau et al. (2007) ⁶⁶¹⁶⁷	201 girls (African American)	8-12	Control (n=83) Exercise (n=118)	20.9 20.9	10 mo	Daily after-school program, 80 min·d ⁻¹ basketball, aerobics, etc.	HR>150 beats·min ⁻¹	2.9 1.4
Kim et al. (2007) ⁶⁷¹⁶⁸	26 boys (Korean)	17.0	Control (n=12) Exercise (n=14)	29.4 29.6	6 wk	Jump rope exercise, 5 d·wk ⁻¹ , 40 min·d ⁻¹	60-90 jumps·min ⁻¹	-1.8 -2.5*
Tjonna et al. (2009) ¹⁴⁷	28 girls 26 boys	14.0	LSE (n=26) Exercise (n=28)	33.3 33.2	3 mo	Walking/running uphill 2 d·wk ⁻¹ , 40 min·d ⁻¹	4 x 4 min intervals at 90%-95% HR _{max} with 3 min active recovery at 70% HR _{max}	-0.02 -0.4
Ben Ounis et al. (2010) ¹⁴⁸	15 boys 17 girls	12-14	Control (n=16) Exercise (n=16)	30.8 31.3	8 wk	Running, jumping, playing with balloon 4 d·wk ⁻¹ , 90 min·d ⁻¹	66% of VO _{2peak}	0.5 -8.0*
Lee et al. (2010) ¹⁴⁹	38 girls	17.0	Control lean (n=20) Control obese (n=7) Exercise (n=11)	19.48 28.02	12 wk	Rope skipping 4 d·wk ⁻¹ , 40-50 min·d ⁻¹	60%-80% of HR _{max}	-1.57 -6.13*†
Lee et al. (2012) ¹⁵⁰	45 boys	12-18	Control (n=13) Exercise (n=16)	33.9 36.6	3 mo	Treadmill, elliptical, or stationary cycling, 3 d·wk ⁻¹ , 40- 60 min·d ⁻¹	40 min at 50% VO _{2 peak} progressed to 60 min at 60%- 75% of VO _{2 peak}	1.1 -2.0†
Lee et al. (2013) ⁷²¹⁷³	44 girls	12-18	Control (n=12) Exercise (n=16)	35.3 32.9	3 mo	Treadmill, elliptical, or stationary cycling, 3 d·wk ⁻¹ , 40- 60 min·d ⁻¹	40 min at 50% VO _{2 peak} progressed to 60 min at 60%- 75% of VO _{2 peak}	-0.25 -2.48
Nonrandomized controlled trials								
Nassis et al. (2005) ⁷³¹⁷⁴	19 girls	9-15	Exercise	26.8	12 wk	3 d·wk ⁻¹ , 40 min·d ⁻¹ running, steps, stair climbing, team sports	HR>150 beats·min ⁻¹	1.1*

Note: Δ, change score. BMI, body mass index; WC, waist circumference; VO_{2 peak}, peak oxygen consumption; HR_{max}, maximal heart rate; HR, heart rate; LSE, lifestyle education; mo, month; wk, week; d, day; min, minute; yr, year

*Significantly different from baseline within each group (p < 0.05).

**Significantly different from baseline within each group (p < 0.01).

†Significantly different from baseline between each group (p < 0.05)

VO₂ peak) with more frequent exercise sessions (≥ 3 sessions/week) for longer durations (≥ 40 minutes/ session) yield greater reductions in waist circumference and/or prevent fat gain in the abdominal region.^{167–173}

Alternatively, very little is known about the influence of resistance training alone without dietary calorie restriction on abdominal fat reduction and waist circumference in adolescents. In a randomized control trial, Benson et al.¹⁷⁷ reported that eight weeks of high-intensity progressive resistance training resulted in small but significant reductions in waist circumference in the training group (-0.8 cm) in comparison with controls (0.5 cm) in normal- weight and overweight youth. Of particular interest, the authors mentioned that the greatest waist circumference reduction was observed in participants with the greatest upper body strength gains and the largest decreases in body fat mass.¹⁷⁷ Similar results were observed in a randomized controlled trial in which obese youth aged 12 to 18 years participated in a progressive 3-month resistance training program.^{172,173} Participants were required to perform 10 different resistance exercises (1-2 sets, 8-12 reps), three sessions per week for a duration of 40 to 60 minutes per session. The intensity was set at $> 60\%$ of baseline one-repetition maximum. Although both sexes had similar exercise adherence of about 97%.^{172,173}, boys significantly reduced their waist circumferences (-3.2 cm)¹⁷² whereas girls showed a more modest reduction (-1.8 cm).¹⁷³ These results suggest that boys and girls seem to respond differently to resistance exercise interventions. From the evidence presented in Table 6, regular resistance exercise may help to attenuate age-related increases in visceral fat and prevent further increases in waist circumference. The independent role of resistance exercise in the reduction of waist circumference is still unclear and further research is warranted.

Table 6. Effect of Resistance or Combined training on Waist Circumference

Reference	Subjects	Age (yr)	Treatment	BMI (kg·m ⁻²)	Duration	Protocol	Exercise intensity	Δ WC (cm)
Randomized controlled trials								
Benson et al. (2008) ⁷⁶¹⁷⁷	46 boys 32 girls	10-15	Control (n=41) Exercise (n=37)	21.9 23.2	8 wk	2d·wk ⁻¹ 2 sets, 11 exercises, 8 reps	80% of 1RM	0.5 -0.8*
Lee et al. (2012) ⁷¹¹⁷²	45 boys	12-18	Control (n=13) Exercise (n=16)	33.9 34.5	3 mo	3 d·wk ⁻¹ , 40-60 min·d ⁻¹ 1-2 sets, 8-12 reps, 10 exercises	> 60% of baseline RM	1.1 -3.2†
Lee et al. (2013) ⁷²¹⁷³	44 girls	12-18	Control (n=12) Exercise (n=16)	35.3 36.4	3 mo	3 d·wk ⁻¹ , 40-60 min·d ⁻¹ 1-2 sets, 8-12 reps, 10 exercises	> 60% of baseline RM	-0.25 -1.82
Nonrandomized controlled trials								
Bell et al. (2007) ⁸²¹⁸³	8 boys 6 girls	12.7	Exercise	31.6	8 wk	Resistance + cycling, 3 d·wk ⁻¹	55%– 65% of 1RM, 2 sets, 10 exercises	-2.3†

Note: Δ, change score. BMI, body mass index; WC, waist circumference; mo, month; wk, week; d, day; min, minute; yr, year; reps, repetitions; RM, one-repetition max

*Significantly different from baseline within each group ($p < 0.05$).

**Significantly different from baseline within each group ($p < 0.01$).

†Significantly different from baseline between each group ($p < 0.05$)

2.9.2 Insulin resistance

Only limited evidence is available regarding the effect of exercise training on insulin resistance in children and adolescents. To our knowledge, two non-randomized controlled trials^{174,178} and eight randomized controlled trials^{168–173,179,180} have reported results on the effects of aerobic exercise on fasting glucose and fasting insulin (Table 7). Nassis et al.¹⁷⁴ examined the effect of a 12-week aerobic exercise training program (3 days/week, 40 min/session, HR $\geq$ 150 bpm) without weight loss on insulin sensitivity in overweight and obese girls aged 9–15 years. Following the training program, the authors observed a significant reduction of 23.3% in the insulin area under the curve following an oral glucose tolerance test, albeit there were no changes in body weight or total adiposity. Similarly, a recent study by Van Der Heijden et al.¹⁷⁸ also demonstrated that a 12-week period of moderate aerobic exercise training (2 days/week, 30 min/session, $\geq$ 70% of VO_{2 peak}) resulted in decreased insulin resistance in post-pubertal obese adolescents. Indeed, the decreased fasting insulin was significantly correlated ($r = 0.40$; $p > 0.05$) with decreased visceral adiposity.

From the eight randomized controlled trials, seven studies^{168–173,180} reported significant improvements in insulin sensitivity measured either from HOMA-IR, an oral glucose tolerance test or a euglycemic clamp. Meyer et al.¹⁸⁰ reported that a 6-month period of aerobic exercise training (3 times/week, 60-90 min/session) without dietary caloric restriction resulted in a significant decrease in fasting insulin (21%) in obese adolescents aged 11–16 years. In another study, Kim et al.¹⁶⁸ found a 34% decrease in insulin resistance after a 6-week jump rope exercise intervention (5 times/week, 40 min/session). Similarly, a study by Tjonna (2009)¹⁶⁹ compared the effect of a multidisciplinary lifestyle education approach with an aerobic interval training program (4 x 4 -min intervals at 90% of HR_{max}) on CVD risk factors in overweight adolescent.

Table 7. Effect of Aerobic training alone on Insulin Sensitivity

Reference	Subjects	Age (yr)	Treatment	BMI (kg·m ⁻²)	IS	Duration	Protocol	Exercise intensity	Δ BMI (kg·m ⁻²)	Δ IS (%)	IS measure
Randomized control trials											
Kelly et al. (2004) ⁷⁸¹⁷⁹	9 boys 11 girls	11.0	Control (n=10) Exercise (n=10)	30.5 32.1	6.0 6.2	8 wk	4 d·wk ⁻¹ , 30-50 min·d ⁻¹	50-80% of VO _{2peak}	-0.1 0.0	-2.8 5.2	2h glucose (OGTT) (mmol/L)
Meyer et al. (2006) ⁷⁹¹⁸⁰	47 boys 49 girls	12-16	Control (n=35) Exercise (n=33)	31.0 29.8	4.4 3.9	6 mo	3 d·wk ⁻¹ , 60-90 min·d ⁻¹ Swimming, games, etc	Progressively intensified as individually tolerated	0.3 -2.6*	11.0 -20.8*	HOMA-IR
Kim et al. (2007) ¹⁴⁶	26 boys (Korean)	17.0	Control (n=12) Exercise (n=14)	29.4 29.6	2.85 2.47	6 wk	5 d·wk ⁻¹ , 40 min·d ⁻¹ Jump rope exercise	60-90 jumps·min ⁻¹	-0.3 -1.0*	-18.2 -33.6*	HOMA-IR
Tjonna et al. (2009) ¹⁴⁷	28 girls / 26 boys	14.0	LSE (n=26) Exercise (n=28)	33.3 33.2	5.5 6.3	3 mo	Walking/running uphill 2 d·wk ⁻¹ , 40 min·d ⁻¹	4 x 4 min intervals at 90%-95% HR _{max} with 3 min active recovery at 70% HR _{max}	-0.2 -0.7*	-5.1 -11.6*	2h glucose (OGTT) (mmol/L)
Ben Ounis et al. (2010) ¹⁴⁸	15 boys 17 girls	12-14	Control (n=16) Exercise (n=16)	30.8 31.3	4.8 5.1	8 wk	Running, jumping, playing with balloon 4 d·wk ⁻¹ , 90 min·d ⁻¹	66% of VO _{2peak}	0.3 -2.0*	-0.8 -11.6*	Fasting blood glucose (mmol/L)
Lee et al. (2010) ¹⁴⁹	38 girls	17.0	Control lean (n=20) Control obese (n=7) Exercise (n=11)	19.48 28.02 27.26	2.51 4.07 6.79	12 wk	Rope skipping 4 d·wk ⁻¹ , 40-50 min·d ⁻¹	60%-80% of HR _{max}	- 0.2 -1.1*	- 59.0 -29.5*	HOMA-IR
Lee et al. (2012) ¹⁵⁰	45 boys	12-16	Control (n=13) Exercise (n=16)	33.9 36.6	2.7 2.2	3 mo	3 d·wk ⁻¹ , 40-60 min·d ⁻¹ Treadmill, elliptical, or stationary cycling	40 min at 50% VO _{2 peak} progressed to 60 min at 60%- 75% of VO _{2 peak}	0.3 -0.3	-3.7 18.2	Euglycemic clamp (mL/kg/min per μU/min)
Lee et al. (2013) ¹⁵¹	44 girls	12-18	Control (n=12) Exercise (n=16)	35.3 32.9	2.7 2.8	3 mo	Treadmill, elliptical, or stationary cycling, 3 d·wk ⁻¹ , 40-60 min·d ⁻¹	40 min at 50% VO _{2 peak} progressed to 60 min at 60%- 75% of VO _{2 peak}	-0.03 -0.46	17.0 32.6**	Euglycemic clamp (mL/kg/min per μU/min)
Non-randomized control trials											
Nassis et al. (2005) ¹⁵²	19 girls	9-15	Exercise	26.8	4.34	12 wk	3 d·wk ⁻¹ , 40 min·d ⁻¹ running, steps, stair climbing, team sports	HR >150 beats·min ⁻¹	-0.1	1.2	HOMA-IR
Van der Heijden et al. (2010) ¹⁵⁶	17 boys 12 girls	15.1	Obese exercise Lean exercise	33.7 20.6	4.9 1.7	12 wk	2 d·wk ⁻¹ , 30 min·d ⁻¹ Treadmill, elliptical, cycle	≥70% of VO _{2peak}	-0.4† 0.1	-16.3*† -11.8	HOMA-IR

Note: Δ, change score. BMI, body mass index; ; VO_{2 peak}, peak oxygen consumption; HR_{max}, maximal heart rate; HR, heart rate; mo, month; wk, week; d, day; min, minute; yr, year; HOMA-IR, homeostatic model assessment – insulin resistance; IS, insulin sensitivity; OGTT, oral glucose tolerance test

*Significantly different from baseline within each group (p < 0.05).

**Significantly different from baseline within each group (p < 0.01).

†Significantly different from baseline between each group (p < 0.05)

After a 3-month intervention, the homeostasis model assessment index for insulin sensitivity (HOMA2-%S, is an updated computer model of HOMA-IR where 100% is considered normal) increased by 23.9% and 10.7% in the exercise and multidisciplinary group (exercise, dietary and psychological advice only), respectively.¹⁶⁹ At the 12-month follow-up, insulin sensitivity measured by HOMA2-%S was still higher than baseline levels by 17.6% and 14.9% in the exercise and multidisciplinary groups, respectively.¹⁶⁹ A research group in the United States recruited 16 boys and 16 girls for their aerobic intervention (3 sessions/week, 40-60 minutes/session, 60%– 75% of $\text{VO}_{2\text{ peak}}$).^{172,173} They assessed insulin sensitivity by using the gold standard euglycemic clamp.^{172,173} Compared with controls, fasting glucose production and hepatic insulin sensitivity did not change significantly for girls in the aerobic group.¹⁷³ However, peripheral insulin sensitivity significantly improved ($p = 0.0007$), even when insulin sensitivity was expressed per unit of free fat mass ($p = 0.001$).¹⁷³ Among boys, no significant changes in insulin secretion were observed for the aerobic group.¹⁷² Again, boys and girls show some similarities but also differ in their responses to the same intervention. Taken together, these studies suggest that aerobic exercise training can decrease insulin resistance independently of diet.

Inconsistent results have also been demonstrated in studies conducted with obese adolescents undergoing a resistance training intervention, as shown in Table 8. Shaibi et al.¹⁸¹ conducted a 16-week resistance training study in overweight or obese male Latino adolescents (aged > 15 years). Insulin sensitivity, as measured by the frequently sampled intravenous glucose tolerance test, increased significantly in the exercise group (2.3 ± 0.3 to $3.2 \pm 0.3 \times 10^{-4} \text{ min}^{-1} \mu\text{U}^{-1} \text{ mL}^{-1}$; $P < 0.05$), a change that was significantly different compared with baseline and the control group. The increase remained significant even after accounting for changes in fat mass

Table 8. Effect of Resistance or Combined training on Insulin Resistance

Reference	Subjects	Age (yr)	Treatment	BMI (kg·m ⁻²)	IS	Duration	Protocol	Exercise intensity	Δ BMI (kg·m ⁻²)	Δ IS (%)	IS measure
Randomized control trials											
Shaibi et al. (2006) ¹⁵⁹	22 boys	15.6 15.1	Control (n=11) Exercise (n=11)	34.6 32.5	1.7 2.3	16 wk	2 d·wk ⁻¹ , < 60 min·d ⁻¹ 2 sets, ~ 15 reps, 10 exercises	~ 97% of 1RM	0.4 0.4	5.9 45.1*†	FSIVGTT (x10 ⁻⁴ /min/μU/mL)
Wong et al. (2008) ¹⁶⁰	24 boys	13-14	Control (n=12) Exercise (n=12)	31.8 30.6	4.5 4.7	12 wk	2 d·wk ⁻¹ , 45-62 min·d ⁻¹ 1-3 sets, 8-25 reps, 4-7 exercises Aerobic stations such as cycle ergometry and/or treadmill	65-85% HR _{max}	-0.1 -1.2*	6.7 0.0	Fasting blood glucose (mmol/L)
Chang et al. (2008) ¹⁶⁴	36 boys 13 girls Chinese	12-14	Control (n=25) Exercise (n=24)	27.1 27.5	7.5 6.8	1 yr	2-5 d·wk ⁻¹ , 60-90 min·d ⁻¹ 0-9 mo: supervised exercise 10-12 mo: no intervention	3-7 METS 145-160 bpm	9 mo/1 yr ≈0.5/0.7 ≈-0.6/0.6	9 mo/1 yr NA/44.0* -48.5*/44.1	HOMA-IR
Benson et al. (2008) ¹⁵⁵	46 boys 32 girls	10-15	Control (n=41) Exercise (n=37)	21.9 23.2	1.1 1.3	8 wk	2d·wk ⁻¹ 2 sets, 11 exercises, 8 reps	80% of 1RM	0.4 -0.01	0.24 (log) 0.11 (log)	HOMA2-IR
Lee et al. (2012) ¹⁵⁰	45 boys	12-16	Control (n=13) Exercise (n=16)	33.9 36.6	2.7 2.9	3 mo	3 d·wk ⁻¹ , 40-60 min·d ⁻¹ 1-2 sets, 8-12 reps, 10 exercises	> 60% of baseline RM	0.3 -0.6*	-3.7 27.6*†	Euglycemic clamp (mL/kg/min per μU/min)
Lee et al. (2013) ¹⁵¹	44 girls	12-18	Control (n=12) Exercise (n=16)	35.3 36.4	2.7 1.8	3 mo	3 d·wk ⁻¹ , 40-60 min·d ⁻¹ 1-2 sets, 8-12 reps, 10 exercises	> 60% of baseline RM	-0.03 -0.28	17.0 0.0	Euglycemic clamp (mL/kg/min per μU/min)
Non-randomized control trials											
Bell et al. (2007) ¹⁶¹	8 boys 6 girls	12.7	Exercise	31.6	8.2	8 wk	3 d·wk ⁻¹ , 60 min·d ⁻¹ 2 sets, 10 exercise + Aerobic (cycling)	55-65% of 1 RM	-0.4	22.2*	Euglycemic clamp M _(lbm) (mg/kg/min)
Van der Heijden et al. (2010) ¹⁶²	6 boys 6 girls	15.5	Exercise	35.3	3.0	12 wk	2 d·wk ⁻¹ , 60 min·d ⁻¹ 2-3 sets, 8-20 reps	~50-85% of 3R max	0.8*	24.0*	Hepatic Insulin sensitivity index

Note: Δ, change score. BMI, body mass index; mo, month; wk, week; d, day; min, minute; yr, year; reps, repetitions; RM, one-repetition max; HOMA-IR, homeostatic model assessment – insulin resistance; IS, insulin sensitivity; OGTT, oral glucose tolerance test; FSIVGTT, standard frequently-sampled intravenous glucose tolerance test

*Significantly different from baseline within each group (p < 0.05).

**Significantly different from baseline within each group (p < 0.01).

†Significantly different from baseline between each group (p < 0.05)

and lean mass. Intergroup comparisons showed that insulin sensitivity in the resistance training group increased by $45.1\% \pm 7.3\%$ versus no change in controls ($0.9\% \pm 12.9\%$, $P < 0.01$). The authors found that the increased insulin sensitivity occurred independently of CRF or body composition changes.¹⁷⁴

Conversely, Wong et al.¹⁸² reported no change in fasting blood glucose after a 12-week resistance training intervention among 24 overweight or obese male adolescents aged 13-14 years. A comparison between pre- and post-training in both groups revealed no significant difference in fasting blood glucose. Similarly, in normal and overweight male and female adolescents aged 10 to 15 years, Benson et al.¹⁷⁷ did not observe a change in insulin sensitivity in the exercise group compared with the non-exercising control group after an 8-week high-intensity progressive resistance training intervention, despite a significant decrease in waist circumference. In another study, a 3-month resistance training intervention (3 sessions/week, 40-60 minutes/sessions, 1-2 sets, 8-12 reps, $> 60\%$ of baseline RM)^{172,173} did not result in changes in fasting glucose production, hepatic insulin sensitivity and peripheral insulin sensitivity among obese girls compared to the non-exercising control group¹⁷³ Unlike the observations by Shaibi et al.¹⁸¹, improvements in insulin sensitivity were associated with exercise-induced increases in skeletal muscle mass as well as cardiorespiratory fitness.¹⁷² Compared to the non-exercising control group, insulin sensitivity improved significantly among boys (0.8 ± 0.2 mL/kg/min per $\mu\text{U/mL}$; $p = 0.009$), even when expressed per unit of fat-free mass.¹⁷² Once again, boys seem to show a better insulin sensitivity response to a resistance exercise intervention than girls. These results are particularly interesting since it was previously reported by Lee that girls responded better to aerobic exercise intervention than boys with regards to insulin sensitivity. In addition, a small non-controlled study ($n=14$) in obese adolescents used a circuit-based program with mixed

aerobic and resistance exercise training stations (3 sessions/week, 60 minutes/session).¹⁸³ After only 8 weeks, authors observed significant increases in insulin sensitivity.¹⁸³ There was no relationship between the degree of improvement in insulin sensitivity and baseline insulin sensitivity.¹⁸³ In another non-controlled single-group study, Van Der Heijden et al.¹⁸⁴ found a $24\% \pm 9\%$ ($P < 0.05$) increase in hepatic insulin sensitivity after 12 weeks of resistance training twice per week in 12 obese Hispanic adolescents. There were no changes in total body fat, visceral fat, hepatic fat, intramyocellular fat content, peripheral insulin sensitivity, fasting glucose, or fasting insulin.¹⁸⁴ Therefore, more studies are warranted to understand the interaction between exercise modalities, sex and insulin sensitivity.

Although the evidence is not conclusive, the observations we have to date show that resistance exercise training is associated with improvements in insulin resistance and thus, should be promoted to children and adolescents. However, future studies with greater sample size (power) are also required to explore the long-term effects of resistance exercise training on insulin resistance and to determine the optimal exercise modality for the most effective strategy to reduce insulin resistance in overweight or obese male and female youth.

2.9.3 Blood pressure

Studies in adults have clearly demonstrated the lowering effect of regular exercise on systolic and diastolic blood pressure. Unfortunately, very few studies have specifically investigated the role of aerobic exercise on blood pressure in youth, while existing studies yield inconclusive results (Table 9). Overall, baseline resting blood pressure seems to influence the magnitude of improvements, where higher baseline values are associated with greater reductions. After an 8-week aerobic training program, Kelly et al.¹⁷⁹ found no significant differences in

Table 9. Effect of Aerobic training alone on Blood Pressure

Reference	Subjects	Age (yr)	Treatment	BMI (kg·m ⁻²)	Blood pressure (mmHg)	Duration	Protocol	Exercise intensity	Δ BMI (%)	BP post-intervention (mmHg)
Randomized control trials										
Kelly et al. (2004) ¹⁵⁷	9 boys 11 girls	11.0	Control (n=10) Exercise (n=10)	30.5 32.1	124/66 125/68	8 wk	4 d·wk ⁻¹ , 30-50 min·d ⁻¹	50-80% of VO _{2peak}	-0.1 0.0	122/68 120/65
Meyer et al. (2006) ¹⁵⁸	47 boys 49 girls	12-16	Control (n=35) Exercise (n=33)	31.0 29.8	121/68.1 117.1/68.3	6 mo	3 d·wk ⁻¹ , 60-90 min·d ⁻¹ Swimming, games, etc	Progressively intensified as individually tolerated	0.3 -2.6*	121.0/68.5 113.1*/68.3
Kim et al. (2007) ¹⁴⁶	26 boys (Korean)	17.0	Control (n=12) Exercise (n=14)	29.4 29.6	129.2/85.0 123.6/79.3	6 wk	5 d·wk ⁻¹ , 40 min·d ⁻¹ Jump rope exercise	60-90 jumps·min ⁻¹	-0.3 -1.0*	124.2/80.8 122.9/81.4
Tjonna et al. (2009) ¹⁴⁷	28 girls / 26 boys	14.0	LSE (n=26) Exercise (n=28)	33.3 33.2	125.0/65.5 128.8/70.4	3 mo	Walking/running uphill 2 d·wk ⁻¹ , 40 min·d ⁻¹	4 x 4 min intervals at 90%-95% HR _{max} with 3 min active recovery at 70% HR _{max}	-0.2 -0.7*	122.5*/67.3 119.4**/64.9**
Ben Ounis et al. (2010) ¹⁴⁸	15 boys 17 girls	12-14	Control (n=16) Exercise (n=16)	30.8 31.3	134.1/79.7 138.7/81.3	8 wk	Running, jumping, playing with balloon 4 d·wk ⁻¹ , 90 min·d ⁻¹	66% of VO _{2peak}	0.3 -2.0*	133.7/80.5 127.1**/72.4**

Note: Δ, change score. BMI, body mass index; ; VO_{2 peak}, peak oxygen consumption; HR_{max}, maximal heart rate; HR, heart rate; mo, month; wk, week; d, day; min, minute; yr, year; BP, blood pressure

*Significantly different from baseline within each group (p < 0.05).

**Significantly different from baseline within each group (p < 0.01).

†Significantly different from baseline between each group (p < 0.05)

systolic and diastolic blood pressure without weight loss in young obese adolescents (mean age = 11 years). Similar results were observed after a 6-week jump rope intervention among obese Korean boys.¹⁶⁸ Limiting factors, such as short studies and normal mean baseline blood pressure values may explain the null findings. On the other hand, Meyer et al. showed a significant decreased in systolic blood pressure (117.0 ± 7.1 mmHg to 113.1 ± 7.7 mmHg; $p < 0.05$) compared with a non-exercising control group (121.0 ± 9.4 mmHg to 121.0 ± 8.6 mmHg) after a 6-month intervention in 47 boys and 49 girls.¹⁸⁰ Another study compared the effects of a multidisciplinary-approach group (combined dietary, exercise, and psychological advices over the course of 12 months) with an aerobic-interval training group (4 x 4 minutes intervals at 90%–95% maximum heart rate (HR_{max}) with 3-minute active recovery at 70% HR_{max}) that occurred twice a week for 3 months.¹⁶⁹ After 3 months, systolic and diastolic blood pressure significantly decreased in the aerobic training group (-9.4 mmHg and -5.5 mmHg respectively; $p < 0.05$) whereas only systolic blood pressure significantly decreased in the multidisciplinary approach group (-2.5 mmHg; $p < 0.05$).¹⁶⁹ However, 9-month post-intervention, mean arterial blood pressure remained 6.2 mmHg lower than baseline only for participants who underwent the aerobic-interval training.¹⁶⁹ In another study, compared to a control group, Ben Ounis et al. found a significant reduction in systolic and diastolic blood pressure (-7.6% and -10.9% respectively; $p < 0.01$) after an 8-week aerobic intervention (4 sessions/week, 90 minutes/session) at an intensity of 66% of VO_{2peak} .¹⁷⁰ Mean systolic blood pressure baseline values were > 130 mmHg for both groups, suggesting that hypertension in youth can be prevented/treated with aerobic exercise training.

To our knowledge, only two studies have investigated the effect of resistance training without caloric restriction on blood pressure (Table 10). A nonrandomized study had 23 male

Table 10. Effect of Resistance or Combined training on Blood Pressure

Reference	Subjects	Age (yr)	Treatment	BMI (kg·m ⁻²)	Blood pressure (mmHg)	Duration	Protocol	Exercise intensity	Δ BMI (kg·m ⁻²)	BP post-intervention (mmHg)
Randomized control trials										
Wong et al. (2008) ¹⁶⁰	24 boys	13-14	Control (n=12) Exercise (n=12)	31.8 30.6	115/71.3 119.6/73.8	12 wk	2 d·wk ⁻¹ , 45-62 min·d ⁻¹ 1-3 sets, 8-25 reps, 4-7 exercises Aerobic stations such as cycle ergometry and/or treadmill	65-85% HR _{max}	-0.1 -1.2*	117.0/70.8 113.8*/71.7
Non-randomized control trials										
Naylor et al. (2008) ¹⁶³	11 boys 12 girls	11-14	Control (n=10) Exercise (n=13)	30.2 32.5	122/58 120/66	8 wk	8 reps, 2 sets 10 Weight-stack machines Circuit based 60 min·d ⁻¹ 3 d·wk ⁻¹	75-90% of 1 RM	-0.2 -0.6	122/59 116*/68

Note: Δ, change score. BMI, body mass index; mo, month; wk, week; d, day; min, minute; yr, year; reps, repetitions; RM, one-repetition max; BP, blood pressure

*Significantly different from baseline within each group ($p < 0.05$)

**Significantly different from baseline within each group ($p < 0.01$)

†Significantly different from baseline between each group ($p < 0.05$)

and female obese youth aged 11 to 14 years who underwent an 8-week resistance training circuit-based intervention.¹⁸⁵ Authors reported a modest reduction in systolic blood pressure (120 ± 2 mmHg to 116 ± 3 mmHg; $p < 0.05$) in the intervention group, compared to the control group (122 ± 2 mmHg to 122 ± 2 mmHg).¹⁸⁵ No changes were reported in diastolic blood pressure for both groups.¹⁸⁵ In a randomized controlled trial, obese males aged 13-14 years participated in a 12-week resistance training intervention. Post intervention, the exercise group (N=12) had a significant drop in systolic blood pressure (119.6 ± 10.8 mmHg to 113.8 ± 7.1 mmHg; $P < 0.05$).¹⁸² In the control group (N = 12), there were no significant differences in systolic and diastolic blood pressure from pre- to post-testing.¹⁸² In summary, it is difficult to draw conclusions from only a few studies, however preliminary results seem promising to reduce blood pressure from regular resistance exercise training in obese youth. More studies investigating the effect of aerobic exercise and/or resistance on blood pressure are warranted.

2.9.4 Blood lipids

Dyslipidemia is associated with a poor quality diet rich in fat. A balanced diet, low in saturated fat, aims to reduce triglyceride concentrations and total cholesterol as well as increase HDL-C concentration. Despite diet being the first line of treatment, some studies have investigated the independent effect of exercise on blood lipids.

As shown in Table 11, there are a limited number of well-controlled studies that examine the effects of aerobic exercise without diet on blood lipid concentration in adolescents.^{168-171,179,180} Kelly et al.¹⁷⁹ randomized 20 adolescents into a control group and an aerobic exercise group. Participants exercised four times per week for 30 to 50 minutes for a period of eight weeks.¹⁷⁹ In the exercise group, HDL-C concentration significantly increased (1.02 ± 0.03

mmol/L to 1.10 ± 0.04 mmol/L; $P < 0.05$) compared to the control group (1.08 ± 0.07 mmol/L to 0.99 ± 0.09 mmol/L).¹⁷⁹ Authors reported no changes in total cholesterol and triglyceride concentrations for both groups.¹⁷⁹ Another study reported an increase in HDL-C concentration (+17.2%, $p < 0.01$) and a decrease in triglycerides concentration (-11.6%, $p < 0.05$) after an 8-week aerobic exercise intervention compared to the control group. This specific exercise program consisted of four weekly 90-minute sessions of running, jumping and playing ball at an intensity of about 66% of VO_{2peak} . Also of note, the exercise group improved its lipid profile as well as mean BMI ($\Delta -2.0$ kg·m⁻²). Similarly, a different study showed that five weekly 40-minute sessions for a period of 6 weeks significantly decrease triglycerides concentrations (1.6 ± 0.2 mmol/L to 0.8 ± 0.1 mmol/L; $p < 0.05$) compared to pre-training concentrations.¹⁶⁸ No changes in total cholesterol and HDL-C concentrations were observed.¹⁶⁸ Likewise, Lee et al. found that a 12-week rope skipping intervention was efficient at decreasing total cholesterol concentration (4.4 ± 0.9 mmol/L to 3.9 ± 0.4 mmol/L; $p < 0.05$) and triglycerides concentrations (1.2 ± 0.4 mmol/L to 0.8 ± 0.3 mmol/L; $p < 0.01$) compared to pre-training concentrations. On the contrary, two studies found no changes in total cholesterol, triglycerides or HDL-C concentrations despite a significant decrease in mean BMI.^{169,180}

Resistance training seems to have very limited effects on plasma blood lipids (Table 12).^{177,182,183,186} Only one study by Chang et al.¹⁸⁶ found an effect of combined resistance and aerobic exercise training on triglycerides and HDL-C concentrations. The intervention consisted of a 9-month exercise intervention supervised by a professional physical education teacher in a school. Twenty-five adolescents aged 12 to 14 years exercised (i.e., running, basketball, standing long jump, rope skipping, taekwondo, sit-and-ups, push-ups and throwing a heavy ball on weekdays, and mountain climbing or swimming on weekends) for 2-5 weekly sessions.

Table 11. Effect of Aerobic training alone on Blood Lipids

Reference	Subjects	Age (yr)	Treatment	BMI (kg·m ⁻²)	Tot. choles (mmol/L)	Trigly (mmol/L)	HDL (mmol/L)	Duration	Protocol	Exercise intensity	Δ BMI (kg·m ⁻²)	Δ Tot. Choles (mmol/L)	Δ Trigly (mmol/L)	Δ HDL (mmol/L)
Randomized control trials														
Kelly et al. (2004) ¹⁵⁷	9 boys 11 girls	11.0	Control (n=10) Exercise (n=10)	30.5 32.1	4.02 3.83	1.00 1.04	1.08 1.02	8 wk	4 d·wk ⁻¹ , 30-50 min·d ⁻¹	50-80% of VO _{2peak}	-0.1 0.0	-0.1 0.2	0.3 0.2	-0.1 0.1†
Meyer et al. (2006) ¹⁵⁸	47 boys 49 girls	12-16	Control (n=35) Exercise (=33)	31.0 29.8	-	1.14 1.41	1.20 1.10	6 mo	3 d·wk ⁻¹ , 60-90 min·d ⁻¹ Swimming, games, etc	Progressively intensified as individually tolerated	0.3 -2.6*	-	-0.1 -0.3	-0.1 0.0
Kim et al. (2007) ¹⁴⁶	26 boys (Korean)	17.0	Control (n=12) Exercise (n=14)	29.4 29.6	4.86 4.12	1.34 1.16	1.17 1.13	6 wk	5 d·wk ⁻¹ , 40 min·d ⁻¹ Jump rope exercise	60-90 jumps·min ⁻¹	-0.3 -1.0*	-0.2 -0.1	-0.2 -0.4*	0.0 0.0
Tjonna et al. (2009) ¹⁴⁷	28 girls 26 boys	14.0	LSE (n=26) Exercise (n=28)	33.3 33.2	-	1.36 1.34	1.23 1.13	3 mo	Walking/running uphill 2 d·wk ⁻¹ , 40 min·d ⁻¹	4 x 4 min intervals at 90%–95% HR _{max} with 3 min active recovery at 70% HR _{max}	-0.2 -0.7*	-	-0.1 -0.2	-0.1 0.1
Ben Ounis et al. (2010) ¹⁴⁸	15 boys 17 girls	12-14	Control (n=16) Exercise (n=16)	30.8 31.3	-	1.62 1.63	1.02 0.99	8 wk	Running, jumping, playing with balloon 4 d·wk ⁻¹ , 90 min·d ⁻¹	66% of VO _{2peak}	0.3 -2.0*	-	0.0 -0.3**	0.0 0.2**
Lee et al. (2010) ¹⁴⁹	38 girls	17.0	Control lean (n=20) Control obese (n=7) Exercise (n=11)	19.48 28.02 27.26	4.1 4.4 4.4	0.7 1.3 1.2	1.4 1.0 1.1	12 wk	Rope skipping 4 d·wk ⁻¹ , 40-50 min·d ⁻¹	60%–80% of HR _{max}	- 0.2 -1.1*	- 0.0 -0.5*	- -0.3 -0.3**	- 0.1 0.1

Note: Δ, change score. BMI, body mass index; ; VO_{2 peak}, peak oxygen consumption; HR_{max}, maximal heart rate; HR, heart rate; mo, month; wk, week; d, day; min, minute; yr, year; Tot. choles; total cholesterol; trigly, triglycerides; HDL, high density lipoprotein

*Significantly different from baseline within each group (p < 0.05).

**Significantly different from baseline within each group (p < 0.01).

†Significantly different from baseline between each group (p < 0.05)

Table 12. Effect of Resistance or Combined training on Blood Lipids

Reference	Subjects	Age (yr)	Treatment	BMI (kg·m ⁻²)	Total choles (mmol/L)	Trigly (mmol/L)	HDL (mmol/L)	Duration	Protocol	Exercise intensity	Δ BMI (kg)	Δ Tot. Choles (mmol/L)	Δ Trigly (mmol/L)	Δ HDL (mmol/L)
Randomized control trials														
Wong et al. (2008) ¹⁶⁰	24 boys	13-14	Control (n=12) Exercise (n=12)	31.8 30.6	4.6 4.5	1.0 1.1	1.2 1.3	12 wk	2 d·wk ⁻¹ , 45-62 min·d ⁻¹ 1-3 sets, 8-25 reps, 4-7 exercises Aerobic stations such as cycle ergometry and/or treadmill	65-85% HR _{max}	-0.1 -1.2*	-0.1 0.2	0.0 -0.1	0.0 0.0
Chang et al. (2008) ¹⁶⁴	36 boys 13 girls Chinese	12-14	Control (n=25) Exercise (n=24)	27.1 27.5	4.3 4.1	1.0 1.3	1.4 1.3	1 yr	2-5 d·wk ⁻¹ , 60-90 min·d ⁻¹ 0-9 mo: supervised exercise 10-12 mo: no intervention	3-7 METS 145-160 bpm	9 mo/1 yr ≈0.5/0.7 ≈-0.6/0.6	9 mo/1 yr NA/0.2 -0.21/0.45	9 mo/1 yr NA/0.5* -0.4/0.2	9 mo/1 yr NA/-0.5* 0.0/0.3*
Benson et al. (2008) ¹⁵⁵	46 boys 32 girls	10-15	Control (n=41) Exercise (n=37)	21.9 23.2	4.3 4.2	0.7 0.8	1.5 1.4	8 wk	2d·wk ⁻¹ 2 sets, 11 exercises, 8 reps	80% of 1RM	0.4 -0.01	-0.11 0.04	Log 0.05 Log 0.16	-0.1 0.1
Non-randomized control trials														
Bell et al. (2007) ¹⁶¹	8 boys 6 girls	12.7	Exercise	31.6	3.85	1.24	1.09	8 wk	3 d·wk ⁻¹ , 60 min·d ⁻¹ 2 sets, 10 exercise + Aerobic (cycling)	55-65% of 1 RM	-0.4	0.22	0.18	0.0

Note: Δ, change score. BMI, body mass index; mo, month; wk, week; d, day; min, minute; yr, year; reps, repetitions; RM, one-repetition max; Tot. choles; total cholesterol; trigly, triglycerides; HDL, high density lipoprotein

*Significantly different from baseline within each group (p < 0.05).

**Significantly different from baseline within each group (p < 0.01).

†Significantly different from baseline between each group (p < 0.05)

After the 9-month intervention, triglyceride concentrations significantly decreased in the exercise group from pre- to post-intervention (1.3 ± 0.67 mmol/L to 0.9 ± 0.29 mmol/L; $p < 0.05$).¹⁸⁶ Three months after the intervention, triglyceride concentrations increased and were similar to baseline values (1.3 ± 0.67 mmol/L to 1.5 ± 0.73 mmol/L).¹⁸⁶ In the control group, triglycerides increased by 50% ($P < 0.05$) and HDL-C decreased by 35% ($P < 0.05$). In the exercise group, there seemed to be a delayed increase in blood lipids, which at 12 months was significantly different from controls ($P < 0.05$).¹⁸⁶ It was concluded that changes in blood lipid concentration in this study may be due to the aerobic component of the study.

In summary, results seem inconsistent and inconclusive. Aerobic exercise seems to have a modest effect on blood lipids whereas resistance training seems to have a limited additive effect. Exercise training typically shows the largest improvements in obese adolescents with the most unfavorable blood lipid profiles at baseline. Most studies recruited participants with a fairly normal blood profile; thus, room for improvement is limited. Moreover, short-term studies may not be able to capture the long-term effects of exercise on blood lipid concentrations.

2.9.5 Summary

Results are summarized in Table 13. Overall, there is evidence to show that aerobic exercise training decreases waist circumference and blood pressure and increases insulin sensitivity in adolescents. Yet, the evidence is not as conclusive for blood lipids. As for resistance training, this exercise modality also decreases waist circumference and increases insulin sensitivity. Again, resistance training seems to have no effect on blood lipids and further research is warranted for its effect on blood pressure.

Table 13. Summary of Effects of Aerobic and Resistance training on the Metabolic Syndrome Parameters

Metabolic syndrome parameters	Aerobic	Resistance
Waist circumference	↓	↓
Insulin resistance	↓	↓
Blood pressure	↓	?
High density lipoprotein concentration	↔	↔
Triglyceride concentration	↓	↔
Total cholesterol	↔	↔

2.10 Exercise intervention studies and the Metabolic Syndrome prevalence

It is important to highlight the fact that most studies in children and adolescents have focused on reducing individual metabolic parameters (i.e. waist circumference, blood pressure, blood lipids and insulin sensitivity). While many studies provided evidence of exercise training on the individual parameters that make up the MetS, they did not account for MetS as a composite score. Of interest, one intervention study used MetS prevalence as an outcome of interest relative to its exposure to a given structured exercise intervention.¹⁷⁰ More specifically, sixteen obese adolescents from various Tanner stages underwent a supervised 8-week training intervention and were compared to a control group (n=16). The exercise intervention occurred four times per week, 90 min/session, and consisted of warming-up, running, jumping and playing with a ball. The exercise intensity was fixed at each participant's heart rate, corresponding to the Fat max value (intensity at maximum fat oxidation) assessed at the first visit (corresponding to 66% of VO_{2peak}). The exercise program adherence was 100%. At baseline, 10 of the 16 participants in the training group and 12 of the 16 participants in the control group were classified as having the MetS based on the IDF definition. After the intervention, none of the 10 participants from the exercise intervention group were diagnosed with the MetS.¹⁷⁰ After the intervention, decreases in systolic (- 7.6%) and diastolic (-10.9%) blood pressure, fasting glucose (-11.6%) and triglyceride levels (-17,8%) were observed in the training group.¹⁷⁰ HDL-C concentration increased post-intervention (+17.2%) in the training group.¹⁷⁰ These significant cardiometabolic improvements are important considering the short duration and the moderate intensity of the exercise intervention. However, data must be interpreted with caution given the small sample size and the questionable feasibility of such an intervention in a real-life setting.

Another study proposed a one-year multidisciplinary intervention to promote changes in sedentary lifestyle and nutritional habits.¹⁸⁷ A total of 83 post-pubertal obese adolescents aged 15 to 19 years (including 37 boys; 36.19 +/- 3.85 kg/m², and 46 girls; 35.73 +/- 4.42 kg/m²) with obesity were included in this study (Tanner stage $\geq$ III). The multidisciplinary intervention consisted of aerobic exercise and nutritional, psychological, and clinical therapy for the management of obesity and MetS. The aim of the nutritional component was to change poor eating habits during the weight loss phase. Energy intake was set at the levels recommended by the Dietary US Reference Intake for participants with low levels of physical activity of the same age and sex.¹⁸⁷ The exercise program consisted of three weekly sessions of 60-minutes of aerobic exercise (walking and stationary cycling). The exercise intensity was set at the cardiac frequency intensity of the ventilatory threshold. The psychological component consisted of discussions about: body image and eating disorders such as bulimia, anorexia nervosa, and binge eating; their symptoms and consequences for health; the relation between feelings and food; familial problems such as alcoholism; and other topics. Based on the WHO definition, the prevalence of MetS in all obese adolescents was 27.16% at baseline.¹⁸⁷ After 12 months, results showed a significant reduction in systolic blood pressure, triglycerides, total cholesterol, fasting insulin, and HOMA-IR compared with baseline ($P < 0.05$).¹⁸⁷ After the intervention, the MetS prevalence was only 8.3%. For boys, the prevalence of the MetS decreased from 35.13% to 13.3%.¹⁸⁷ For girls, the prevalence of MetS decreased from 19.46% to 4.54%.¹⁸⁷ Despite a large sample size, the 1-year multidisciplinary intervention was a very aggressive intervention and it is difficult to distinguish the effect of exercise from the other intervention strategies. Nonetheless, this multidisciplinary program was effective at reducing MetS prevalence among obese adolescents and future research should examine this further.

2.11 Conclusion

To our knowledge, we have reviewed all the studies that investigated the effects of an exercise intervention on the prevalence of MetS in obese adolescents. One study focused on aerobic training alone and the other study used a multidisciplinary approach, making it difficult to compare results. Moreover, both studies used different pediatric MetS definitions. One of the difficulties in interpreting the current literature with regards to exercise and MetS is the relative paucity of trials examining different exercise modalities on MetS as a composite, versus examining the role of different exercise modalities on the individual components of the MetS. There are currently no available data on large samples that have evaluated the impact of different exercise modalities on individual components and prevalence of MetS in obese adolescents.

CHAPTER III

METHODS AND RESULTS

ARTICLE I:

Effects of aerobic training, resistance training, or both in obese adolescents with the metabolic syndrome: the HEARTY randomized controlled trial

Effects of aerobic training, resistance training, or both in obese adolescents with the metabolic syndrome: the HEARTY randomized controlled trial

Alexandrine Frappier, BSc¹; Angela S. Alberga, PhD²; Ronald J. Sigal, MD, MPH³; Glen P. Kenny, PhD⁴; Steve Doucette, MSc⁵; Denis Prud'homme, MD, MSc^{1,6}✉

¹ School of Human Kinetics, Faculty of Health Sciences,

² Faculty of Education,

³ Ronald J. Sigal, MD, MPH,

⁴ School of Human Kinetics, Faculty of Health Sciences,

⁵ Department of Community Health and Epidemiology

⁶ Institut de Recherche de l'Hôpital Montfort

Address for correspondence: Dr. Denis Prud'homme

Vice-President Research, Montfort Hospital
Scientific Director, Institut de recherche de l'Hôpital Montfort

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ABSTRACT

Importance: Among overweight and obese adolescents, there is little evidence regarding the effect of exercise training for metabolic syndrome, and more specifically which modality is the most optimal treatment option .

Objective: To determine the effects of Aerobic training, Resistance training, and Combined training on the prevalence of metabolic syndrome in overweight and obese adolescents.

Design: Secondary analysis of data from the HEARTY trial, which was a randomized parallel-group controlled trial.

Setting: Community-based exercise facilities in Ottawa (Ontario) and Gatineau (Québec), Canada.

Participants: Previously-inactive post-pubertal adolescents (N=304) aged 14-18 years old (Tanner Stage IV-V) with Body Mass Index $\geq$ 85th percentile for age and sex. A sub-sample (n=49) was identified as having the metabolic syndrome based on the International Diabetes Federation definition.

Intervention: After a 4-week low-intensity exercise run-in period, 49 participants were randomized to 4 groups for a 22-week week: Aerobic training (N=11), Resistance training (N=12), Combined aerobic and resistance training (N=10), or non-exercising Control (N=16). All participants received dietary counseling with a daily energy deficit of 250 kcal.

Main Outcome(s) and Measure(s): The primary outcome was the prevalence (% of participants) of the metabolic syndrome defined by the International Diabetes Federation at baseline and 6 months. We hypothesized that Aerobic and Resistance training respectively would

yield greater decreases in the prevalence of the metabolic syndrome than no exercise (Control), and Combined training would show greater decreases than Aerobic or Resistance training alone.

Results: There were no significant changes in the prevalence of MetS between groups, however, significant improvements in MetS parameters were observed within groups; with Aerobic training, there was a significant decrease in waist circumference (-3 cm) and systolic (-11 mmHg) and diastolic (-5 mmHg) blood pressure from baseline to post-intervention. Resistance training significantly decreased body mass index (-1.5 kg/m^2), percentage body fat (-2%), waist circumference (-5 cm) and systolic (-10 mmHg) and diastolic (-6 mmHg) blood pressure from baseline to post-intervention. Combined aerobic and resistance training significantly decreased triglyceride concentrations (-0.7 mmol/L) and increased high density lipoprotein concentration (+0.04 mmol/L) compared to baseline. The Control-diet significantly decreased systolic blood pressure (-7 mmHg) and fasting insulin (-24.9 $\mu\text{IU/mL}$) when comparing pre- and post-intervention.

Conclusions: Exercise, regardless of modality, not statistically effective for reducing the prevalence of MetS but did improve MetS component features. Future research should examine the effects of various exercise intensities and durations to determine the optimum strategy to deliver cardiometabolic health benefits and reduce the prevalence of MetS in overweight and obese adolescents.

Trial Registration: ClinicalTrials.Gov NCT00195858

<http://clinicaltrials.gov/show/NCT00195858>, September 12, 2005 (Funded by the Canadian Institutes of Health Research).

INTRODUCTION

The metabolic syndrome (MetS) is a cluster of risk factors that include impaired glucose tolerance, arterial hypertension, hyperinsulinemia, increased triglyceride levels, reduced high-density lipoprotein cholesterol and high waist circumference.¹ The syndrome links metabolic abnormalities into a single pathophysiological construct, suggesting that the cluster is driven by the consequences of peripheral insulin resistance.¹ Initially, MetS was primarily documented in adults and was linked to an increase risk of cardiovascular morbidity and mortality.² Considering the increased incidence and prevalence of childhood obesity³ and the strong link between obesity and MetS,⁴ it is not surprising that MetS has been identified in a sub-group of overweight or obese, leading to fears of earlier onset of chronic disease such as type 2 diabetes, cardiovascular disease and premature mortality.⁴

Given the well-supported physiological benefits associated with exercise training in adolescents,^{5,6} advocating exercise training is of paramount importance for individuals with MetS. What is fundamental to most exercise recommendation statements⁷ is the endorsement of aerobic training, and more recently, resistance training.⁸ Resistance training appears to be an important component in the prevention and management of chronic diseases given evidence that suggests that the combination of both exercise modalities may be more beneficial than aerobic exercise alone.^{9,10} In fact, it was shown in the Diabetes Aerobic Resistance Exercise study (DARE) trial that the Combined (aerobic and resistance) exercise intervention was more effective in reducing hemoglobin A1c and some parameters associated with MetS in adults with type 2 diabetes than Aerobic or Resistance training alone.⁹

Epidemiological studies demonstrated that physical activity levels are inversely associated with the prevalence of MetS in adolescents.¹¹ Furthermore, some studies conducted in healthy children using accelerometers as an objective tool to measure physical activity found an

inverse relationship between physical activity levels and the prevalence of cardiometabolic risk factors, independent of age, gender and body mass index (BMI) or adiposity.¹²⁻¹⁷ While many pediatric exercise trials examined various parameters of MetS as the primary outcomes, to our knowledge, only two studies have evaluated the effect of exercise training on the prevalence of MetS, that is, by examining a composite score of the respective parameters comprising MetS.^{18,19}

One study focused on the effect of aerobic training alone¹⁹ and the other study used a multidisciplinary approach¹⁸ that included nutritional, psychological, and clinical therapy as well as aerobic exercise for the management of obesity and MetS. Both randomized controlled trials were effective in reducing the prevalence of MetS. However aerobic training was the only exercise modality investigated; resistance training was not included. This pair of studies had certain limitations, notably the first study¹⁹ had a small sample size and the feasibility of the intervention in a real-life setting is questionable. Despite a larger sample size in the second study,¹⁸ the 1-year multidisciplinary intervention was a very aggressive intervention and it was difficult to distinguish the effect of exercise from the other intervention strategies. Therefore, the aim of the present study was to determine the effects of Aerobic training, Resistance training, Combined aerobic and resistance training, and a non-exercising-Control on the prevalence of MetS in participants (i.e., % of participants) of the Healthy Eating Aerobic and Resistance Training in Youth (HEARTY) trial. We hypothesized that Combined aerobic and resistance training would predict a greater decrease in the prevalence of MetS after a 6-month exercise intervention compared to Aerobic, Resistance and Control-diet conditions alone.

METHODS

Design

This paper is a secondary analysis of the HEARTY trial data.²⁰ The HEARTY study was a randomized controlled trial using a parallel-group design. Details on the rationale, design and methods have been described elsewhere.²¹ The HEARTY study was approved by the Research Ethics Boards at the Children's Hospital of Eastern Ontario (CHEO) and the Ottawa Hospital, Canada. All participants (and parents, for participants under the age of 16 years) provided written informed consent.

Participants

Male and female post-pubertal adolescents (Tanner stage IV-V) aged 14-18 years with a BMI $\geq$ 95th percentile for age and sex (<http://www.cdc.gov/growthcharts>) or $\geq$ 85th percentile with an additional risk factor for diabetes or cardiovascular disease a) fasting glucose > 6.0 mmol/L, b) 2-hour plasma glucose 7.8-11.1 mmol/L after 75g oral glucose (impaired glucose tolerance), c) fasting triglycerides > 1.7 mmol/L, d) fasting plasma insulin > 105 pmol/L, e) high density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L, f) low density lipoprotein cholesterol > 3.0 mmol/L, g) total cholesterol/high density lipoprotein ratio $> 90^{\text{th}}$ percentile, or h) first-degree relative with type 2 diabetes, and waist circumference $\geq 75^{\text{th}}$ percentile for their age and sex) were eligible to participate in the HEARTY trial. Participants were excluded if they: engaged in exercise more than twice weekly for over 20 minutes per session within four months of beginning the HEARTY study (excluding routine school physical education classes), had diagnosed type 1 diabetes, uncontrolled hypertension or any illness or disability rendering the exercise intervention inadvisable. They were also excluded if they showed signs of an eating disorder and/or experienced a weight change (increase or decrease of $\geq 5\%$) in the two months prior to enrollment in the study. The use of performance-enhancing medication or any other

medication that could affect body composition (e.g. metformin, oral contraceptives) was permitted only if the dose had been stable over the previous two months and if the dose was to remain unchanged throughout the trial.

Based on the pediatric MetS definition of the International Diabetes Federation (Table1), a sub-sample of participants was identified.²² The IDF definition requires a WC > 90th percentile for age and sex and at least two additional metabolic abnormalities: triglycerides > 1.7 mmol/L, HDL-C < 1.03 mmol/L, systolic blood pressure $\geq$ 130 mmHg, diastolic blood pressure $\geq$ 85 mmHg, fasting plasma glucose $\geq$ 5.6 mmol/L or known type 2 diabetes. Details of the methods and protocol for the HEARTY trial are available elsewhere (reference); only the methods used for this secondary analysis are described here.

Run-in period (weeks 1-4)

Prior to the start of the intervention, participants began a run-in period to test exercise session compliance that was comprised of supervised moderate-intensity exercise training four times weekly for four weeks. They were required to attend at least 80% of prescribed sessions, each of which consisted of 15-30 minutes of aerobic exercise at 65% of measured maximum heart rate as well as 1 to 3 sets of 15 repetitions of seven different resistance exercises. Details of the exercise training program have been described previously.²¹

Randomization

After the run-in phase, qualified participants were randomized to. by an exercise specialist using a telephone-based central randomization program (IVRS, VBvoice v5.3, Pronexus, Ottawa, Canada) thereby informing participants of their group assignments but

allowing the research coordinator to remain blinded. Randomization was in permuted blocks, stratified by sex and degree of overweight (BMI between 85th-94th percentile versus $\geq$ 95th percentile). A total of 304 participants were randomized to four groups for a 22-week intervention: Aerobic training (N=75), Resistance training (N=78), Combined aerobic and resistance training (N=75), or non-exercising Control (N=76).

Intervention

Participants in all four groups attended an initial visit with a registered dietitian to discuss weight and diet history, fast food consumption and current eating habits. They received dietary counseling at baseline, 3- and 6-months to promote healthy eating with a maximum daily energy deficit of 250 kcal. In addition to the dietary counseling, participants in all three exercise groups were asked to attend the gym four times per week. The Aerobic group performed exercise on a cycle ergometer, elliptical or treadmill. The exercise intensity and duration increased progressively from 20 minutes to a maximum of 45 minutes per session. Intensity was monitored using heart rate monitors (Polar Electro Oy, Kempele, Finland), which were used to adjust workloads to achieve the target heart rates during exercise. The initial intensity was set at 65% and was gradually increased to 85% of maximum heart rate. The Resistance group completed seven exercises using weight machines or free weights. Intensity was progressively increased from two sets of 15 repetitions to three sets of 8 repetitions at the maximum resistant that could be moved eight times (8-RM). The Combined group performed the full Aerobic and Resistance training program during each session. After completing the run-in phase, participants in the Control group were asked to revert to their pre-study activity levels for 22 weeks. They followed the same dietary advice as participants in the exercise groups.

Outcomes and Measurements

Body Composition

Body composition was assessed by magnetic resonance imaging (MRI) (General Electric, 1.5 tesla scanner, version signal 11 with echo speed gradients, Milwaukee, WI) at baseline and 6 months. The participants laid prone to acquire whole body cross-sectional images using protocols by Ross.^{7,8} The MRI images were analyzed using Slice-O-Matic software v. 4.3 (Tomovision, Magog, Canada).

Anthropometric measurements

Weight (kg), height (cm), BMI, waist circumference (cm) and blood pressure were measured at baseline, 3 and 6 months by the research coordinator. Weight and height were measured using a Health O Meter manual scale (Health O Meter, Continental Scale Corp., Bridgeview, Illinois). BMI was calculated by weight (kg) / height (m²). Waist circumference was measured at the middle distance between the last floating rib and the iliac crest using a retractable ergonomic measuring tape (Seca GmbH & Co Kg, Hamburg, Germany).

Cardiometabolic Risk Factors

All blood samples for measuring fasting plasma glucose, insulin and lipid concentrations, except for the Oral Glucose Tolerance Test (2-h post load plasma glucose), were collected at baseline, 3 and 6 months. These measurements were obtained following a 12-hour fasted conditions. Participants also refrained from vigorous physical activity and the use of anti-inflammatory or other medications for 24 hours before the blood sampling.

Total cholesterol, triglycerides and high-density lipoprotein cholesterol levels were measured by enzymatic methods on a Beckman-Coulter LX20 analyzer (Beckman Instruments, Brea, California). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation²³. Insulin resistance was also estimated from fasting plasma glucose and insulin concentrations using the homeostatic model assessment – insulin resistance (HOMA-IR)²⁴ defined as:

$$\text{HOMA-IR} = (\text{fasting glucose mmol/L} \times \text{fasting insulin } \mu\text{U/mL}) / 22.5$$

Patients were considered insulin resistant if their HOMA-IR score was ≥ 3.16 .²⁵

Statistical Analysis

Categorical data was presented as frequencies with percentages and continuous data as medians and interquartile range. Differences between intervention modalities on the prevalence of continued metabolic syndrome at 6 months post intervention was assessed using the chi-square test statistic. Differences in anthropometric and cardiometabolic risk factors at 6 months was assessed within intervention groups using the non parametric Wilcoxon signed-rank test. Between group differences for all exercise groups vs. the control group was assessed using the Non parametric Wilcoxon rank-sum test.

RESULTS

The primary aim of the HEARTY trial was to determine the effects of a 6-month aerobic training, resistance training, and combined training on percent body fat in overweight and obese adolescents.^{20,21} In this paper are presented the secondary data analysis results from the HEARTY trial participants who met the criteria of MetS according to the IDF definition²². Of the

304 participants who were randomized [sex: males = 91 (30%) vs. females = 213 (70%); mean age: 15.6 ± 1.4 years; BMI $\geq 95^{\text{th}}$ percentile = 282 participants (93%)], 65 (21.4%) participants were found to have MetS: Aerobic training (n = 15), Resistance training (n = 19), Combined aerobic and resistance training (n = 12) and Control (n = 19).

Figure 1 presents the effect of the different intervention modalities on the prevalence of the metabolic syndrome, which was obtained by dividing the number of participants with MetS at 6 months post-intervention by total number of participants with MetS at baseline. At baseline, all participants (100%) had metabolic syndrome. From baseline to 6-months, the prevalence of MetS decreased to 36.4% in the Aerobic training group, to 33.3% in the Resistance training group, to 20.0% in the Combined training group and to 56.3% in the Control training group. However, there were no significant differences regarding the change in MetS prevalence over time between groups.

The prevalence of each component of the MetS following the 6-month interventions is presented in Table 2. In general, there was a decrease in the prevalence of the MetS component features for the different exercise training modalities and for the dietary counseling intervention with the exception of no changes in fasting glucose and HDL-C in the Combined and Control group respectively. From baseline to 6-months, the prevalence of high blood pressure decreased in the Aerobic training group (from 63.6% to 9.1%), in the Resistance training group (from 66.7% to 33.3%), in the Combined group (from 20% to 0%) and in the Control group (from 31.3% to 18.8%). From baseline to 6-months, the prevalence of high triglyceride concentration decreased in the Aerobic training group (from 54.6% to 45.5%), in the Resistance training group (from 58.3% to 50.0%), in the Combined group (from 90.0% to 20.0%) and in the Control group (from 81.3% to 56.3%). From baseline to 6-months, the prevalence of low HDL-C concentration

decreased in the Aerobic training group (from 72.7% to 63.6%), in the Resistance training group (from 75.0% to 41.7%), in the Combined group (from 90.0% to 80.0%) and in the Control group (from 93.8% to 81.3%). From baseline to 6-months, the prevalence of high fasting plasma glucose concentration decreased in the Aerobic training group (from 27.23% to 9.1%), in the Resistance training group (from 25.0% to 8.3%), and in the Control group (from 12.5% to 0%) and remained the same in the Combined group (10.0%).

Given that there was a non- significant difference in the prevalence of the MetS between the training intervention groups and the control group in post-intervention, we divided the participants in two sub-groups based on the presence (N = 19) or absence of the MetS (N = 30) after the intervention. The average compliance score (% of sessions attended) in participants with and without MetS post-intervention was not statistically different. The mean percent scores were 48.7 (33.8) in the no MetS and 38.2 (39.7) in the MetS group (P = 0.33).

Anthropometry and Cardiometabolic Risk Factors

Table 3 presents the effect of different training modalities on anthropometric indices and cardiometabolic risk factors. At baseline, there were no significant intergroup differences on all variables. Within each intervention group, there was a significant increase in height from baseline to post-intervention (all $p < 0.05$). In the Aerobic training group, there were significant decreases from baseline to post-intervention within group in systolic blood pressure (-9 mmHg; $p = 0.001$) and diastolic blood pressure (-6 mmHg; $p = 0.004$). There were no significant differences in waist circumference, triglyceride concentrations, high density lipoprotein cholesterol concentration, fasting glucose level, fasting insulin level and HOMA-IR score from baseline to 6-months. In the Resistance training group, there were significant decreases from

baseline to 6-months within group in waist circumference (-4.5 cm; $p = 0.002$), body mass index (-0.9 kg/m^2 ; $p = 0.03$), systolic blood pressure (-8.5 mmHg; $p = 0.02$) and diastolic blood pressure (-5.5 mmHg; $p = 0.04$). There were also significant decreases in waist circumference (-4.4 cm; $p = 0.04$) compared to the Control group. There were no significant decreases in triglyceride concentration, high density lipoprotein cholesterol concentration, fasting glucose level, fasting insulin level and HOMA-IR score from baseline to 6-months. In the Combined group, there was a significant decrease in triglyceride concentration (-0.9 mmol/L ; $p = 0.002$) and a significant increase in high density lipoprotein cholesterol concentration ($+0.04 \text{ mmol/L}$; $p = 0.047$) from baseline to post-intervention within group. However there were no significant decreases in waist circumference, systolic and diastolic blood pressure, fasting glucose level, fasting insulin level and HOMA-IR score from baseline to 6-months. In the Control group, there were significant decreases from baseline to post-intervention within group in systolic blood pressure (-7.5 mmHg ; $p = 0.009$) and fasting glucose level (-0.25 mmol/L ; $p = 0.046$). There were no significant decreases in waist circumference, diastolic blood pressure, triglyceride concentration, high density lipoprotein concentration, fasting insulin concentration, and HOMA-IR score from baseline to post-intervention.

DISCUSSION

At baseline, the prevalence of MetS in the HEARTY cohort of participants was 21.4%. It is similar to previous findings from a recent systematic review,²⁶ which found the median prevalence of MetS in obese pediatric populations to be 29.2% (ranging from 10% to 66%).

The primary findings from the current study revealed no statistical differences in the prevalence of MetS within and between Aerobic, Resistance, Combined and Control groups after

the 6 –month intervention. At baseline, all participants had metabolic syndrome. After 6-month, the prevalence of MetS was reduced in the Aerobic (36.4%), Resistance (33.3%), Combined (20.0%) and Control (56.3%). The lack of statistical difference may be attributed to a lack of statistical power. Although the MetS is a relatively new clinical diagnostic indicator in adolescents, there is evidence to support that Aerobic training beneficially affects MetS component features. It has previously been shown that Aerobic training decreases fasting triglyceride levels^{19,27,28}, increases the HDL-C concentrations,^{19,29} reduces waist circumference,^{19,27,28,30} lowers blood pressure,^{19,31,32} and either lowers fasting glucose^{19,31–33} and/or prevents the increases associated with inactive lifestyles. In the present study, although Aerobic training did not significantly improve all five features of the IDF MetS criteria, there were significant decreases in waist circumference and systolic and diastolic blood pressure among participants in this group. Overall with Aerobic training, there was a decrease in the prevalence of MetS in our participants by -63.6%, (from 11 participants at baseline with MetS to 4 participants with MetS at 6-months), which is in agreement with previous studies that showed decreases of 68-100%.^{18,19} One study used the prevalence of MetS as an outcome of interest following exposure to an 8-week structured exercise intervention in obese adolescents aged 12 to 14 years.¹⁹ At baseline, 10 of 16 participants in the training group and 12 of 16 participants in the control group were classified as having the MetS based on the IDF definition.²² After the intervention, all 10 participants from the exercise intervention group no longer met the classification of the metabolic syndrome.¹⁹ Another study proposed a 1-year multidisciplinary intervention to promote changes in sedentary lifestyle and nutritional habits in obese adolescents aged 15 and 19 years.¹⁸ The multidisciplinary intervention consisted of aerobic exercise and nutritional, psychological, and clinical therapy for the management of obesity and the metabolic

syndrome. At baseline, using the World Health Organization definition,³⁴ the prevalence of MetS in all adolescents with obesity (n = 83) was 27.16%.¹⁸ After the intervention, the MetS prevalence was only 8.3%.¹⁸

While clinical exercise intervention trials support the efficacy of aerobic training in reducing the prevalence of MetS and its individual parameters, less is known about Resistance and Combined aerobic and resistance training, especially in overweight and obese adolescents. In the literature, Resistance training has been consistently shown to be superior to Aerobic training for improving muscular strength and lean body mass.⁶ In the present study using a subsample of participants with MetS, our findings for the resistance group showed a significant decrease in BMI, percentage body fat and waist circumference, which is consistent with previous studies^{30,35}. We also observed a significant reduction in systolic and diastolic blood pressure following Resistance training. This is in agreement with the literature showing that blood pressure is normalized in obese adolescents after a short (2-3 months) period of Resistance training.^{36,37} Combined aerobic and resistance training significantly decreased triglyceride concentrations and increased HDL-C concentrations.

Based on our results, exercise, regardless of training modalities, led to a decrease in the number of participants with MetS after the 6-month intervention. This is clinically relevant since obese adolescents who have MetS are at greater risk of developing type 2 diabetes and cardiovascular diseases. Despite a lack of statistical significance, many participants were no longer classified as having MetS after the 6-month exercise intervention. Overall across all groups, there were 49 participants with MetS at baseline. After the intervention, only 19 participants retained the diagnosis; 4 participants in the Aerobic group, 4 participants in the Resistance group, 2 in the Combined group and 9 in the Control group. This trend has

previously been observed in adults. Specifically, the findings of Health Benefits of Aerobic and Resistance Training in individuals with type 2 diabetes (HART-D) and the Studies of a Targeted Risk Reduction Intervention Through Defined Exercise (STRRIDE) suggested that Aerobic training and Combined aerobic and resistance training are equally effective for reducing the prevalence of MetS in adults with³⁸ or without type 2 diabetes.³³ In both HART-T and STRRIDE trials, participants were not given any dietary counseling nor were they expected to alter their current diet to isolate the independent effect of exercise.^{10,39} Interestingly, the prevalence of the MetS decreased in both trials among participants in the Aerobic and Combined aerobic and resistance training groups, whereas those undertaking Resistance training and Control conditions showed no significant reduction in the metabolic syndrome. Arguably, the volume and/or intensity of resistance training may not have been sufficient to affect changes in MetS component features similar to aerobic training. Nonetheless, further research is warranted to confirm if different exercise modalities yield similar decreases in the prevalence of the MetS and whether a combination of aerobic and resistance training may be more effective, particularly in adolescents.

According to the IDF definition,²² waist circumference is the *primum movens* (define) for the diagnostic of the metabolic syndrome.²² This assertion is based on the evidence that abdominal fat, especially visceral fat accumulation, plays an essential role in the development of multiple cardiometabolic risk factors associated with components of MetS in adults and adolescents.^{40–43} Some researchers suggest that visceral fat is one of the driving forces underpinning the metabolic syndrome, namely through associated insulin resistance, hyperinsulinemia and sub-chronic inflammation state.^{41–43} Visceral fat is typically assessed with a simple clinical measurement of waist circumference that moderately reflects abdominal fat⁴⁴

and visceral fat area.⁴⁵ In the present study, we observed a reduction in waist circumference in Aerobic (-2.5 cm), Resistance (-4.8 cm), Combined (-3.6 cm) and Control (-1.3 cm) but only in the Aerobic and Resistance training alone were the reductions statistically significant respectively. In women, it has been shown that a reduction in waist circumference of at least 3.0 cm has a significant beneficial effect in reducing the prevalence of MetS.⁴⁶ Therefore, the decrease observed in waist circumference in all exercise groups (from -2.5 to -4.8 cm) in our study with adolescents would appear to be clinically important, especially in the absence of a significant decrease in weight²⁰ and this has potential importance from a clinical point of view. The decrease in waist circumference, along with concomitant reductions in visceral fat, may contribute to improve the adolescents' cardiometabolic profile.⁴⁶

In the present study, we observed a decrease in the prevalence of each MetS parameters for all intervention groups. In other words, systolic and diastolic blood pressure, triglycerides and HDL-C concentration levels, waist circumference and fasting glucose levels decreased albeit non-significantly. On the one hand, greater reductions were noted in blood pressure, triglyceride levels and fasting glucose levels. On the other hand, results of the exercise interventions were less pronounced regarding HDL-C concentration, with a high number of participants (n = 49) still meeting the MetS criterion at 6-months post-intervention. This could be partly explained by evidence regarding the limited effect exercise training and dietary counselling have on HDL-C concentrations in youth.^{5,6} In the current paediatric literature, diet is the main factor affecting HDL-C concentrations.⁴⁷

The current secondary analysis study has methodological strengths and limitations. Strengths include the randomized controlled design of the HEARTY trial, the concurrent measurement of cardiometabolic health outcomes using gold standard methods for the

measurement of body composition (e.i. MRI). The main limitation includes the size of the subsample (n= 49) from the total sample (n= 304), which was limited by the number of participants who met the paediatric IDF criteria of the MetS and who had complete baseline and post-intervention data. In addition, because this was a supervised exercise intervention, our findings cannot be generalized to unsupervised exercise training programs in adolescents.

This exploratory study summarizes results regarding the relative effect of different exercise training modalities and diet counselling on the cardiometabolic health of overweight and obese adolescents with the metabolic syndrome. The lack of statistical power limits our ability to draw solid conclusions; however, there is meaningful evidence supporting the recommendation of aerobic and/or resistance training combined with dietary counselling as potentially efficacious interventions to reduce the prevalence of the MetS in adolescents with obesity. Future research must examine the effects of various exercise intensities and durations to determine the optimum dose that will deliver cardiometabolic health benefits and reduce the prevalence of MetS in overweight and obese adolescents.

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APPENDIX

Table 1. Criteria used by the International Diabetes Federation²² for diagnosing the Metabolic Syndrome (MetS) in Children and Adolescents

Criteria	International Diabetes Federation (aged 10 to < 16 years)
Central adiposity measured by waist circumference	90 th percentile of waist circumference or adult cutoff if lower
Triglycerides	≥ 150 mg/dl (> 1.7 mmol/L)
High density lipoprotein cholesterol	< 40 mg/dl (< 1.03 mmol/L)
Systolic blood pressure	≥ 130 mmHg
Diastolic blood pressure	≥ 85 mmHg
Fasting plasma glucose	≥ 100 mg/dl or diagnosed type 2 diabetes mellitus (> 5.6 mmol/L)
MetS Diagnosis	Central adiposity plus at least 2 of other components

Table 2. Prevalence of Metabolic Syndrome at baseline and post-intervention based on the International Diabetes Federation²²

Parameter	Aerobic		Resistance		Combined		Control	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Waist circumference $\geq 90^{\text{th}}$ percentile	11 (100%)	10 (91.7%)	12 (100%)	10 (83.3%)	10 (100%)	9 (90%)	16 (100%)	16 (100%)
Blood pressure (SBP ≥ 130 mmHg and DBP ≥ 85 mmHg)	7 (63.6%)	1 (9.1%)	8 (66.7%)	4 (33.3%)	2 (20%)	0 (0%)	5 (31.3%)	3 (18.8%)
Triglycerides (≥ 150 mg/dL)	6 (54.6%)	5 (45.5%)	7 (58.3%)	6 (50%)	9 (90%)	2 (20%)	13 (81.3%)	9 (56.3%)
High density lipoprotein cholesterol (< 40 mg/dL)	8 (72.7%)	7 (63.6%)	9 (75%)	5 (41.7%)	9 (90%)	8 (80%)	15 (93.8%)	13 (81.3%)
Fasting glucose (≥ 100 mg/dL)	3 (27.3%)	1 (9.1%)	3 (25%)	1 (8.3%)	1 (10%)	1 (10%)	2 (12.5%)	0 (0%)
Subjects with MetS (WC + ≥ 2 components)	11 (100%)	4 (36.4%)	12 (100%)	4 (33.3%)	10 (100%)	2 (20%)	16 (100%)	9 (56.3%)

Data are number and percentage

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; MetS, metabolic syndrome

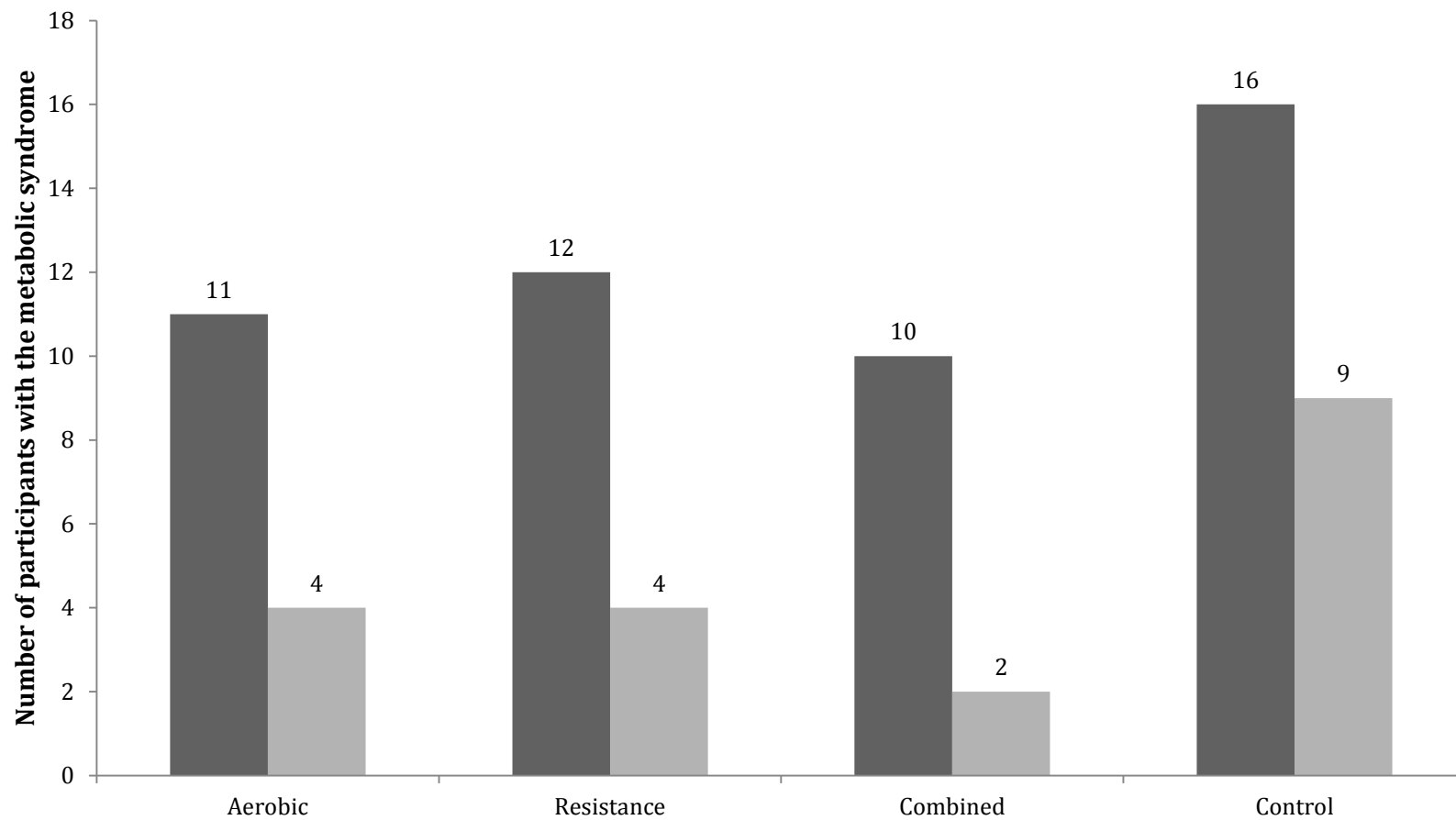


Figure 1. Number of participants with the metabolic syndrome at baseline and post-intervention based on the International Diabetes Federation²²

Table 3. HEARTY Participants' anthropometric and metabolic parameters at baseline and post-intervention
Data are medians (IQR)

Parameter	Aerobic (n=11)		Resistance (n=12)		Combined (n=10)		Control (n=16)	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Weight (kg)	108 (86.4 - 112.6)	103.2 (86 - 118.5)	114.4 (99.7 - 124.4)	109.6 (99.8 - 120.7)	103 (89.3 - 109.6)	101.7 (93 - 118.1)	110.3 (98 - 121.2)	113.8 (97 - 119.6)
Height (cm)	175 (161.5 - 175)	175.5 (162.5 - 176.2)*	174.5 (169.4 - 181.1)	174.3 (170 - 183.5)*	169 (164.5 - 175.2)	170.8 (166.5 - 183)*	168 (163.5 - 175.7)	168 (165 - 177.1)*
BMI (kg/m ²)	36.2 (32.8 - 36.8)	35.5 (32.4 - 38.1)	36.8 (34.1 - 38.9)	36.1 (31.2 - 39.1)*	35.4 (32.8 - 37.3)	34.9 (32.8 - 36.6)	37.9 (33.7 - 41)	37.7 (33.3 - 40.9)
Body fat (%)	48.2 (45.1 - 53.2)	48.1 (42.1 - 51.6)	46.5 (45.2 - 51.6)	45.4 (41.4 - 51.8)*	48.3 (43.3 - 50.3)	46.5 (41.6 - 48.3)	49.2 (45.5 - 53.6)	49 (43.1 - 52.5)
Waist circumference (cm)	101 (89.5 - 113)	98 (89 - 103)	103 (101 - 118)	101 (96.3 - 109.8)*†	101.1 (94 - 106.5)	96 (94 - 104)	107.8 (96.5 - 111.3)	106.3 (97.7 - 109.3)
Systolic blood pressure (mmHg)	123 (114 - 131)	111 (108 - 116)*	128 (121 - 141)	119.5 (108.5 - 129)*	117 (108 - 120)	111 (110 - 115)	119.5 (114 - 129.5)	112 (104.5 - 119)*
Diastolic blood pressure (mmHg)	84 (75 - 88)	80 (70 - 81)*	82.5 (74 - 85.5)	74.5 (69.5 - 80)*	76 (69 - 80)	77.5 (74 - 79)	80.5 (76 - 84.5)	75 (70 - 80.5)
Triglycerides (mmol/L)	1.8 (1.2 - 2.3)	1.7 (1.2 - 2.2)	1.8 (1.3 - 2.2)	1.6 (1.1 - 2.1)	2.2 (1.9 - 2.5)	1.4 (1.3 - 1.6)*	2.1 (1.8 - 2.4)	1.8 (1.4 - 2.4)
Total cholesterol (mmol/L)	4.7 (3.7 - 5.3)	4.3 (3.4 - 5)	4.5 (4 - 5.1)	4.4 (3.9 - 4.8)	4.7 (3.8 - 5.1)	4.4 (4.1 - 4.7)	5.2 (4.1 - 5.5)	4.7 (4.1 - 5.6)
High density lipoprotein cholesterol (mmol/L)	0.9 (0.8 - 1.1)	0.9 (0.8 - 1.2)	1 (0.8 - 1)	1.1 (0.8 - 1.1)	0.9 (0.8 - 1)	0.9 (0.9 - 1)*	0.9 (0.8 - 0.9)	0.8 (0.8 - 1)
Fasting glucose (mmol/L)	5.3 (4.8 - 5.7)	5.2 (5 - 5.2)	5.4 (4.6 - 5.8)	5.2 (4.8 - 5.5)	5.1 (4.8 - 5.2)	5 (4.7 - 5.4)	5.3 (4.9 - 5.4)	5 (4.8 - 5.1)*
Fasting insulin (μIU/mL)	117 (70 - 147)	121 (88 - 152)	128 (102 - 149)	87 (69 - 168)	96 (79 - 135)	82 (70 - 129)	149 (91 - 280)	155 (106 - 199)
HOMA-IR	4.1 (2.3 - 4.5)	4 (2.9 - 5)	4.1 (3 - 5.1)	3 (2.4 - 5.7)	3 (2.4 - 3.7)	2.6 (2.1 - 4.8)	4.8 (3.1 - 10)	4.8 (3.3 - 6.1)

Note: BMI, body mass index; HOMA-IR, Homeostatic model assessment for insulin resistance.

* P < 0.05; pre- vs. post-intervention within group

† P < 0.05; different from diet-only

ARTICLE II:

The metabolic syndrome in children and adolescents: a critique

¹Alexandrine Frappier, ²Stasia Hadjiyannakis, ^{1,3}Denis Prud'homme

¹School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada, K1N 6N5; ²Healthy Active Living and Obesity Research Group, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada; ³Institut de Recherche de l'Hôpital Montfort (D.P.), Ottawa, Ontario, K1K 0T2, Canada

Address for correspondence:

Dr Denis Prud'homme

Vice-President Research, Montfort Hospital

Scientific Director, Institut de recherche de l'Hôpital Montfort

Abstract

The metabolic syndrome (MetS) is a cluster of several cardiometabolic risk factors related to insulin resistance. The prevalence of MetS is about 3% in the whole population but it can be as high as 66% among overweight and obese children. There is no consensus concerning its definition and its clinical value in children and adolescents. Most of the proposed definitions in pediatrics are derived from three main organizations: World Health Organization, National Cholesterol Education Program and Adult Treatment Panel III and the International Diabetes Federation. Due to the differences in the criteria and cutoff values proposed, the prevalence of the MetS varies according to the definition that is used. Many concerns have been raised in the literature: (a) the primum movens of MetS is not shared by all, (b) the assessment of certain MetS criteria such as waist circumference is not standardized, (c) some of the criteria used to define MetS are not clinically validated. Specifically, critical cutoffs to detect either underlying conditions or the increased risk of developing MetS are not yet known, and in some cases the criteria and / or cutoffs proposed are misleading since they do not use the same ‘pathological’ cutoff values for the MetS component features, and (d) the stability over time of the diagnosis of MetS in childhood may not be as straightforward as in adulthood due to transitional hormonal changes associated with puberty. The first step towards a standard definition of MetS is to determine the true clinical purpose of identifying the metabolic syndrome in the pediatric population.

Keywords: Metabolic syndrome, children, adolescents, critic, concerns

Words: 3714

Abbreviations

CVD	Cardiovascular disease
IDF	International Diabetes Federation
MetS	Metabolic syndrome
NCEP	National Cholesterol Education Program
T2D	Type 2 Diabetes
WHO	World Health Organization

Metabolic syndrome: historical aspects and definitions

In the early 20th century, it was repeatedly observed that metabolic changes were associated with the onset of cardiovascular disease (CVD) and type 2 diabetes (T2D).(1) In 1988, Reaven et al(2) introduced a new term, “syndrome X”, for the coexistence of impaired glucose tolerance, arterial hypertension, hyperinsulinemia, increased triglycerides and reduced high-density lipoprotein cholesterol. Reaven proposed a conceptual framework, which linked apparently unrelated cardiometabolic abnormalities into a single pathophysiological construct, suggesting that this cluster of metabolic abnormalities is driven by consequences of peripheral insulin resistance.(2) In 1999, the World Health Organization (WHO) was the first organization to propose a standard definition of the metabolic syndrome (MetS).(3) In response, the European Group for the Study of Insulin Resistance defined the “insulin resistance syndrome” with modifications of the WHO definition.(4) Two years later, the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) proposed a new, simpler definition to implement in research and clinical practice.(5) In 2005, the American Heart Association and the National Heart lung and Blood Institute introduced a revised definition of the metabolic syndrome.(6) The same year, the International Diabetes Federation (IDF) published yet another version of the MetS definition, with central adiposity as the core component to identify individuals at risk of T2D and cardiovascular diseases.(7)

Still, the underlying mechanisms that tie the observed cardiometabolic abnormalities together remain unclear. Since the first attempt to define MetS, this area of research has progressed, especially in adults. However, research relating to the MetS in children and adolescents moved at a much slower pace. Given the increase in the incidence and prevalence of childhood obesity(8) and the strong link between obesity and MetS,(9) the MetS has been

identified in a sub-group of overweight or obese youth, leading to fears of earlier onset of chronic disease such as T2D, CVD and premature mortality.(9) However, many researchers criticized MetS definitions, stating that ‘too much critically important information is missing to warrant its designation as a syndrome’.(17) Debate about the pediatric definition of MetS still persists, yet there is little hope of reaching true agreement unless there is consensus regarding the clinical purpose and usefulness of the term. Thus, family physicians and pediatricians are faced with the dilemma of whether to use MetS as a simple tool to identify children and adolescents who are at higher risk of developing co-morbidities of T2D and CVD despite criticisms that exist. From a research and clinical standpoint, it is important to develop tools to identify children at risk of cardiometabolic abnormalities that will contribute to our understanding of the origins of cardiometabolic risk and enhance our ability to improve their health in their current stage of life and/or as adults.

The utility of defining MetS in the pediatric population is questionable: some researchers suggest that such definitions are inappropriate for this specific population. They raise concerns regarding the use of this collection or syndrome of cardiometabolic risk factors in children as a composite rather than focusing on the risk factors individually.(18, 19) Nevertheless, it is imperative to acknowledge that the underlying pathophysiology that leads to obesity-driven metabolic abnormalities may develop in childhood and manifest only in adulthood.(20) This highlights the importance of early screening to identify children and adolescents at risk of cardiometabolic complications and the application of preventive strategies.(21)

Complexity of defining the metabolic syndrome in childhood

There is currently no general consensus regarding the definition of MetS in children and adolescents. The application of several pediatric MetS definitions has led to some confusion

regarding the true epidemiology of this syndrome. Many definitions have been proposed by various research groups; one review published in 2007 found 46 different pediatric definitions across 27 studies.(10) Most proposed classifications were derived from three adult definitions proposed by the WHO, NCEP and IDF(11) and they have been used in several pediatric studies in order to quantify the prevalence of the metabolic syndrome.(11) Thus, it is not surprising that the prevalence of the MetS varies considerably (0% to 66%) between studies depending on the population's characteristics (e.g. body mass index, ethnicity, age groups, etc) and the definition that is employed.(11) Nonetheless, studies have reported a higher prevalence of MetS among obese children and adolescents compared to their leaner peers.(12–16)

In a recent systematic review, 85 papers which applied variants of the NCEP, IDF and WHO criteria were reviewed (See table 1).(11) The definitions by these three main organizations share common features: measure of the degree of central obesity by means of waist circumference, two dyslipidemia components (elevated triglycerides and low high density lipoprotein cholesterol levels), elevated blood pressure and an index of glucose-insulin homeostasis.(3, 5, 22) However, a unified concept of the MetS in children is lacking. There are biases by some leading authorities towards using the MetS to identify children and adolescent at higher risk of developing T2D while others are more focused on cardiovascular risk. For example, T2D or insulin resistance conditions are main criteria for MetS diagnosis according to the WHO(3) whereas waist circumference is the main criterion for diagnosis according to IDF.(22) One study found that using the NCEP definition led to identifying half as many children and adolescents as having MetS as did the WHO definition in the same population.(23) This demonstrates the incompatibility between different MetS definitions that have been proposed, which identify different cardiometabolic phenotypes. This could have significant impact on research findings and for the development of screening and clinical practical guidelines.

After many revised MetS definitions proposed, some relevant issues still persisted concerning the concept of the MetS more generally in the pediatric population: (a) the *primum movens* (primary cause) of MetS is not agreed upon by all researchers and clinicians, (b) the assessment of certain pathological features of the MetS, such as waist circumference measurement, is not standardized, (c) some of the criteria used to define MetS are not clinically validated in a way that critical cutoffs to identify underlying conditions or the increase risk of developing MetS are not yet known and in some cases the criteria and / or cutoffs proposed are misleading since they do not use the same ‘pathological’ cutoff values for the included risk indices and (d) the stability over time of the diagnosis of MetS in childhood may not be as straightforward as in adulthood due to puberty. The following paragraphs will expand on these points of contention.

Primum movens

Even with common features, the updated pediatric NCEP and IDF criteria supposedly identify the same individuals as having MetS.(24) From a logical point of view these definitions greatly differ. According to NCEP criteria, an adolescent with MetS has elevated triglycerides, high blood pressure and elevated fasting glucose.(5) Yet, according to the IDF definition, this patient cannot be considered to be suffering from MetS unless he/she has central obesity.(22) Similarly, the WHO requires assessment of insulin resistance or alteration of the glucose metabolism in order to diagnose the patient as having the MetS.(3) Hence, a patient with elevated waist circumference and blood pressure as well as dyslipidemia does not have the MetS according to the WHO. These definitions do not always identify the same patients as suffering from the same condition despite using the same terminology to describe different clinical phenotypes. In general, the NCEP definition is more heavily based on cardiometabolic risk,

whereas the WHO employs a disease-based definition in which glucose homeostasis abnormalities are thought to be crucial components.(3, 23) There is a general consensus regarding the importance of an altered glucose-insulin homeostasis as the key component underlying the diagnosis of the metabolic syndrome.(3, 5, 22) However, the NCEP and IDF definitions estimate glucose homeostasis alteration only by means of a fasting plasma glucose value,(5, 22) whereas the WHO definition accepts any type of measurement of insulin resistance.(3)

Overall, pediatric definitions of the MetS differ because they do not recognize the same observations as being the defining elements of the syndrome. That is, the *primum movens* is not consistent across definitions and this requires an evaluation to determine the true clinical and research purpose of identifying children and adolescents with metabolic syndrome. Is the syndrome defined by counting the number of patients with a coexistence of impaired cardiometabolic features such as glucose intolerance, hypertension, hyperinsulinemia, increased triglycerides and reduced high-density lipoprotein cholesterol? Or is MetS best defined by proposing a pathogenetic mechanism that explains the association between various impaired cardiometabolic conditions? In general, there is evidence in the literature demonstrating that it is difficult to view MetS as a single distinctive disease because various definitions have led to the collection of different criteria under the same MetS label. It is important to remember that the term MetS was initially proposed on the basis of finding a common underlying mechanism, in this case insulin resistance, and not for clinical purposes(25). Still, clinical definitions of MetS had a primary goal of identifying individuals at increased risk of developing T2D and cardiovascular diseases(26).

However, the application and validity of MetS in clinical practice is questionable among the adult population since other tools such as the Framingham score tool appear to be more useful than the MetS as predictors of CVD and stroke,(25, 27, 28) albeit less predictive of type 2

diabetes.(29) Areas under the receiver-operating characteristic curves for the Framingham score vs. the number of metabolic abnormalities were 0.68 vs. 0.59 for coronary heart disease, 0.60 vs. 0.70 for T2D, and 0.66 vs. 0.55 for stroke ($P < .001$ for all).(29) In other words, the Framingham score is a better predictor of coronary heart disease and stroke than MetS, yet MetS better predicts T2D than the Framingham score. Those two tools (the Framingham score and MetS) likely carry different importance in terms of outcome prediction. In other words, it is not clear which three components among the features of the MetS (i.e., blood lipids, blood pressure, waist circumference and fasting plasma glucose) should be used to make the diagnosis (the *primum movens*) and whether the combination of any three features is equally predictive of the risk of T2D and cardiovascular diseases. If we applied the same reasoning to the pediatric population, we need to ask the question, how the clinical management of a child with two MetS criteria would be different from that of a child with a diagnosis of MetS? The ability to develop powerful, effective interventions toward the improvement of people's health may bring new ethical responsibilities. If we want to ensure that limited healthcare resources are appropriately used, we must begin with a clear clinical purpose of what MetS, as a composite is, and define it as such. Up to now, studies have shown that addressing each component of the cluster individually has comparable clinical and predictive outcomes as addressing all components as an entity.(27, 31) Future debates aimed at reaching a consensus concerning the MetS definition in the pediatric population should not be based on the associations between particular groups of cardiometabolic conditions. Instead, progress should be made on improving our knowledge of current pathophysiological mechanisms underlying the presence of a systematic cluster of cardiometabolic conditions that together suggest a higher T2D and CVD risk than any single or other combination of cardiometabolic risk factors.

Standardization of assessment

Standards for assessing certain MetS components in children and adolescents are lacking. Waist circumference is the main criteria for the diagnostic of the MetS based on the IDF definition.(22) Central adiposity correlates with waist circumference in adolescents ($r = 0.88$; $p < 0.01$) and is associated with cardiometabolic complications (ranging from $r = 0.14$ to 0.64 ; $p < 0.01$). (32–34) At present, there is no standard on how to measure waist circumference in children and adolescents. In spite of this, reference values of waist circumference exist only for some pediatric populations such as Americans, Mexican-Americans and African-American, limiting the use of the IDF waist circumference criteria to multiple ethnic populations, as it is the case for the adult population.(35) A recent study compared four waist circumference measurement sites that are commonly used in research in overweight boys and girls and demonstrated that different sites are not uniformly associated with cardiometabolic risk factors.(36) At present, there is no consensus on age-, gender- and ethnic-group-specific cutoffs for waist circumference related to cardiometabolic factors and morbidity in children and adolescents. Standardization of waist circumference measurement procedures is important since the use of different percentiles can increase or decrease measurement sensitivity, specificity and its predictive value and yield different prevalence rates of MetS within and between different populations. Fortunately, more standard references for waist circumference are being introduced for different populations.(37–41)

Dichotomous discrete variable categorizations

Dichotomizing discrete variables in order to categorize abnormalities simplifies the diagnosis of MetS in everyday clinical practice, but it discards crucial information about the magnitude of cardiometabolic risk factors and consequently the risk of morbidity and

mortality.(42) Therefore, creating dichotomies is not necessarily the optimal choice for diagnosis or risk prediction. All of the proposed MetS definitions share the notion that all components have an equal “value” in estimating cardiometabolic risk. This is problematic given that cardiovascular risk factors, such as the degree of obesity or elevated fasting glucose and triglycerides, represent continuous variables for which their level risk are not necessarily associated in a linear fashion.(43) The lack of specific pediatric normative cutoff values for each of the MetS component features makes it difficult to define the syndrome in a clear, unbiased way that is supported by underlying patho-physiological mechanisms as well as risk evaluation based on data from longitudinal studies. Instead of dichotomous variables, some investigators have suggested the use of a continuous risk score (i.e. z-score) to improve the value and clinical utility of diagnosing MetS in children and adolescents.(44) The continuous score emphasizes the importance of using population-derived percentile cutoffs (age, gender and ethnicity specific) for each MetS component rather than phenotype-based absolute cutoffs that occur during growth until sexual maturity is reached.

Unfortunately, not all criteria are defined in percentiles in the literature.(3, 5, 22) For example, the updated IDF consensus for defining MetS in children and adolescents aged between 10 and 16 years uses absolute cut-offs for blood pressure (≥ 130 or ≥ 85 mmHg or using an antihypertensive drug), lipids (triglycerides > 1.7 mmol/L, HDL cholesterol below 1.03 mmol/L or using a hypolipemiant drug) and glycemia (fasting glycemia > 5.6 mmol/L), whereas only waist circumference is assessed by percentile ($\geq 95^{\text{th}}$ percentile for age and sex).(22) The use of single cut-off values (regardless of gender, sex and ethnicity) may be clinically easier to use, however it is less sensitive in identifying children at risk of developing T2D and cardiovascular diseases(42). For example, in late adolescence, baseline fasting triglycerides level and its change within a 5-year follow-up period may predict the development of T2D and CVD even when

values are below the MetS cutoff values,(45) something that may not be detected with cut-off values. Another issue is the application of the same MetS criteria cutoff to populations with different ethnicities. This could lead to under-estimating the risk of T2D in children and adolescents from ethnic minorities who are more prone to develop type 2 diabetes (e.g. Hispanic).(46, 47) Similarly, considering that the distribution of blood lipid values is different in African American compared to Caucasians children, the use of the current cutoff values may lead to under-diagnosing MetS in the African American pediatric population despite the fact that they are more at risk of cardiovascular diseases.(48) In addition, there are ethnic differences in patterns of lipid partitioning in insulin-responsive tissues such as muscle and liver.(49) Hence, individuals with similar degrees of obesity but from different ethnic groups may differ in regards to their state of peripheral insulin sensitivity. In other words, anthropometric and metabolic components of the MetS should be age and ethnicity specific and derived from data from a given population. It is thus not surprising that researchers have not yet reached consensus on the MetS criteria cutoff values. To date, no robust clinical and statistical methods have been used to define cut-off values of MetS criteria in the pediatric population.(18)

Overtime stability of the MetS diagnosis

Adolescence is a transitional period characterized by dynamic physiological and psychosocial changes in boys and girls.(50) With the onset of puberty marking the passage from childhood to adolescence there is a tremendous rate of growth, changes in body composition, insulin sensitivity, puberty, maturation, and fitness that are driven by biological processes. Consequently, the pathophysiological basis and characteristics of MetS are also influenced by the impact of growth and puberty.(51, 52) Puberty status and timing are known to markedly influence adipose tissue disposition, lipids and glucose metabolism homeostasis.(53–55) This has

to be taken into consideration when defining MetS criteria as well as their respective cutoff values in adolescents. Concerns have been raised regarding the stability of the clinical diagnosis of MetS over time during childhood and adolescence.(56, 57) Goodman et al. (56) followed a cohort of 1098 teenagers over a 3-year period and using the American Heart Association/National Heart, Lung, and Blood Institute definition for adults and IDF definitions in adolescents they found that a categorical diagnosis of MetS was unstable over time. Up to half of the children with MetS at baseline failed to meet the criteria at follow-up, despite consistent risk factor clustering.(56) Thus, the clinical significance of the MetS seems to be reduced during adolescence. Goodman et al.(56) suggested that due to MetS measurement variability and/or the physiological effects of growth and puberty on glucose-insulin homeostasis there is a high degree of diagnostic instability over time and therefore MetS classification might not be an effective method for cardiometabolic risk stratification in pediatrics. Moreover, Gutstafson et al.(57) found that among obese children and adolescents aged 6 to 17 years, only 30% and 45% of those with baseline diagnostic of MetS were confirmed after 60-day and 1.5 year follow-ups, respectively. These results are very striking considering the very short duration of follow-up in these studies. The stability of the MetS diagnosis over time has been shown to be tightly associated with weight fluctuations and changes in insulin sensitivity in obese adolescents.(9) These observations of the instability of the MetS diagnosis in adolescents in a few studies may be dependent on (a) the hormonal changes associated with puberty that induce a significant reduction in peripheral insulin sensitivity, (b) the pubertal growth spurt that may result in significant body shape changes and an increase in blood pressure and (c) the limited reproducibility and reliability of single measurements of blood pressure, lipids and glucose parameters. None of the currently accepted definitions include a subject's puberty status and timing in the classification.

Conclusion

With the increased prevalence of obesity among children and adolescents since the middle of the twentieth century, there is a threat for millions of children to develop cardiometabolic abnormalities, thus becoming a major public health concern.(58) The metabolic syndrome is a cluster of metabolic abnormalities often associated with obesity that are believed to have a common underlying mechanism (insulin resistance). The metabolic syndrome remains a controversial topic within research and medical communities. The *primum movens* of MetS is not shared across all proposed definitions and this leads to the identification of heterogeneous populations despite application of the same label. In addition, the measurement procedures must be standardized to facilitate cross-population comparison. Moreover, determining cutoff values for the components of MetS should be based on a statistical approach by selecting a particular percentile, based on age and gender and ethnicity that represents a strong relationship between the component and an intermediary or long term cardiometabolic outcome. Finally, puberty should be taken into consideration when defining and diagnosing MetS since the stability of the diagnosis of MetS is questionable during this crucial growth period and transitional phase of physiological and cardiometabolic alteration and adaptation. Nevertheless, the first step towards a standard definition of MetS is to define the true clinical purpose of the metabolic syndrome in the pediatric population.

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Table 1. Different Criteria Used by Organization for Diagnosing the Metabolic Syndrome in Children

Criteria	WHO	IDF (aged 10 to < 16 years)	NCEP
Central adiposity measured by WC	> 95 th percentile for age and sex	90 th percentile of WC or adult cutoff if lower	Waist $\geq$ 102cm (M) or $\geq$ 88cm (F)
Triglycerides	< 10 years of age: > 105 mg/dL (> 1.2 mmol/L) > 10 years of age: > 136 mg/dL (> 1.5 mmol/L)	$\geq$ 150 mg/dl (> 1.7 mmol/L)	$\geq$ 150 mg/dl
HDL-C	< 35 mg/dL (< 0.9 mmol/L)	< 40 mg/dl (< 1.03 mmol/L)	< 40mg/dl (M) or < 50mg/dl (F)
Total cholesterol	> 95th percentile	-	-
Systolic blood pressure	> 95 th percentile for age and sex	$\geq$ 130 mmHg	$\geq$ 130 mmHg
Diastolic blood pressure	> 95th percentile for age and sex	$\geq$ 85 mmHg	$\geq$ 85 mmHg
Fasting plasma glucose	Abnormal glucose homeostasis, such as fasting hyperinsulinemia, impaired fasting glucose, and impaired glucose tolerance ($\geq$ 110 mg/dl)	$\geq$ 100 mg/dl or known type II DM (> 5.6 mmol/L)	$\geq$ 110 mg/dl or treatment for DM
Diagnosis	Insulin resistance + $\geq$ 2 components	Central adiposity plus at least 2 of other components	$\geq$ 3 components

Note: WHO, World Health Organization; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program; WC, Waist Circumference; M, Males; F, Females; HDL-C, High Density Lipoprotein-Cholesterol.

CHAPTER IV

GENERAL CONCLUSIONS

4.1 Conclusions

The primary purpose of the first article was to determine the effects of Aerobic training, Resistance training, Combined aerobic and resistance training, or a non-exercising-Control on the prevalence (%) of MetS in overweight and obese adolescents aged 14-18 years old from the Healthy Eating Aerobic and Resistance Training in Youth (HEARTY) trial. The results of our study demonstrate that exercise, regardless of the modality, was not statistically effective for reducing the prevalence of MetS. However, Aerobic training, Resistance training and Combined training effectively improved some of MetS component features. After 6-months, Aerobic training significantly decreased waist circumference and systolic and diastolic blood pressure. Resistance training significantly decreased body mass index, percentage body fat, waist circumference and systolic and diastolic blood pressure. Combined aerobic and resistance significantly decreased triglyceride concentrations and increased high density lipoprotein concentration. The Control group significantly decreased systolic blood pressure and fasting insulin.

These findings can be used as guidelines to design future exercise interventions and to calculate sample size. Although limited in scope, to our knowledge this is study to examine the effects of both exercise modalities or their combination on the prevalence of metabolic syndrome. A trend was observed as all exercise modalities decrease the prevalence of participants with MetS despite no statistical differences. This may be due to statistical power. Future research is warranted and the effects of various exercise intensities and durations should be explored.

The objective of the second article was to raise concern and questions regarding the use of MetS in children and adolescents. International Diabetes Federation criteria for MetS are necessarily dichotomous for clinical purposes, whereby if WC is $\geq 95^{\text{th}}$ percentile for age and sex

specific plus $\geq$ of the 5 metabolic variables are higher than a certain threshold, a subject is considered to have the metabolic syndrome. For the purpose of measuring effects of an intervention, a continuous score, rather than a series of dichotomous scores, might be more accurately represent and detect overall metabolic improvements. Perhaps the use of a continuous z-score of all MetS variables may be more appropriate approach to monitor changes in MetS and its parameters over time.

Many paediatric MetS definitions exist in the literature and there is currently no gold standard. The first step towards a standard definition of MetS is to define the true clinical purpose of the metabolic syndrome in the pediatric population. It would need to address a few concerns and verify the overtime stability of the diagnosis in childhood due to transitional hormonal change associated with puberty and its effect on cardiometabolic profile. The first step towards a standard definition of MetS is to define the true clinical purpose of the metabolic syndrome in the pediatric population.

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