Physical activity and cardiorespiratory fitness in the prevention and management of type 2 diabetes in youth

by

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Abstract

Background. Estimates are that one third of children will develop type 2 diabetes in their lifetime. Lifestyle changes, including physical activity are established effective tools to prevent and manage type 2 diabetes in adults but the evidence in youth is lacking. Several key questions remain including: (1) Can youth with type 2 diabetes achieve target glycemic control with lifestyle changes alone? (2) Is type 2 diabetes in youth associated with low physical activity and cardiorespiratory fitness? and (3) What is the appropriate intensity of physical activity to reduce the risk for type 2 diabetes in overweight youth?

Methods. Three studies were conducted to answer these questions: i) a retrospective chart review to determine the clinical efficacy of lifestyle monotherapy to manage glycemia in youth newly diagnosed with type 2 diabetes; ii) a cross sectional study to test the association between physical activity, cardiorespiratory fitness and type 2 diabetes risk factors in youth; and iii) a randomized controlled trial of physical activity designed to determine the training intensity required to improve insulin resistance and reduce intrahepatic lipid content in overweight youth at risk for type 2 diabetes (interim results presented).

Results. Study A. Over 50% of youth newly diagnosed with type 2 diabetes and glycosylated hemoglobin ≤9% were able to achieve target glycemic control for as long as 12 months with lifestyle monotherapy. Study B. Physical activity levels (4905±2075 vs. 6937±2521 vs. 8908±2949 steps/day, $p<0.05$ vs. healthy weight youth) and cardiorespiratory fitness (23.4±5.9 vs. 26.7±6.0 vs. 36±6.6 ml/kg/min,

p<0.05) are lower in youth with type 2 diabetes versus overweight and healthy weight controls. Intrahepatic lipid is significantly higher (13.0%±14.1 vs. 5.6%±6.2 vs. 1.4%±1.4, p<0.05) and inversely associated with insulin sensitivity (r = -0.40, p<0.001). Study C. Interim analyses present promising trends from a 6-month physical activity intervention.

Conclusions. Lifestyle therapy can be an effective tool to manage new-onset diabetes in certain youth, and is also important in the prevention of type 2 diabetes in youth. Youth with type 2 diabetes are characterized by low levels of physical activity and cardiorespiratory fitness. Interim results are presented from a randomized controlled physical activity trial that we anticipate at completion will provide promising data to guide development of community-based programming to reduce risk for type 2 diabetes in overweight youth.

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List of Abbreviations

AIR	Acute insulin response
ACR	Albumin-creatinine ratio
ALT	Alanine aminotransferase
AMPK	5'AMP-activated protein kinase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
BF	Body fat (%)
BMI	Body mass index (kg/m^2)
BPM	Beats per minute (heart rate)
CANPLAY	Canadian Physical Activity Levels Among Youth
Chol	Total cholesterol
Cs	Caucasian ethnicity
DERCA	Diabetes Education Resource for Children and Adolescents
DBP	Diastolic blood pressure
DPP	Diabetes Prevention Program
DPS	Diabetes Prevention Study
DXA	Dual energy x-ray absortiometry
FFA	Free fatty acid
FFM	Fat free mass
FN/M	First Nation / Metis ethnicity
FSIVGTT	Frequently sampled intravenous glucose tolerance test

G_F	Fasting glucose
GLUT-4	Glucose transporter type 4
HbA_{1c}	Glycosylated hemoglobin
HBSC	Health Behaviours in School-Age Children survey
HDL	High density lipoprotein
^{1}H-MRS	Proton magnetic resonance spectroscopy
HNF-1α	Hepatic nucleotide factor 1 alpha
	GG (wildtype), GS (heterozygote), SS (homozygote).
HOMA	Homeostatis assessment model (-IR, 'of insulin resistance')
HR	Heart rate
HRmax	Maximal heart rate
HRR	Heart rate reserve
HW	Healthy weight (control group)
I_F	Fasting insulin
IGT	Impaired glucose tolerance
ISPAD	International society for pediatric and adolescent diabetes
O	'Other' ethnicity
OGTT	Oral glucose tolerance test
LDL	Low density lipoprotein
LSE	Lifestyle education
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy / (^{1}H-MRS)
NGT	Normal glucose tolerance

POWER Trial	Physical activity for OverWEight youth at Risk for diabetes
PPM	parts per million
QUICKI	Quantitative insulin sensitivity check index
RE	Energy restriction (diet)
RER	Respiratory exchange ratio
RM	1 repetition max
RPE	Rate of perceived exertion (/20)
SBP	Systolic blood pressure
STRRIDE	Studies of a targeted risk reduction intervention through defined exercise
T2DM	Type 2 diabetes
TG	Triglycerides
TODAY study	Treatment Options for type 2 Diabetes in Adolescents and Youth
VO_{2peak}	Peak oxygen uptake (achieved during fitness test)
YMCA/YWCA	Young Men's / Women's Christian Association

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Chapter 1

General Introduction

Introduction

Type 2 diabetes mellitus (T2DM) is a growing public health concern worldwide. While the prevalence of type 2 diabetes in adults has nearly doubled over the last three decades (Wild, Roglic et al. 2004; Gregg, Cheng et al. 2007); the trends in youth are even more alarming (Bloomgarden 2004; Pinhas-Hamiel and Zeitler 2007), and parallel the dramatically increasing rates of obesity in youth. In the mid to early 1980's, type 2 diabetes accounted for 0-4% of new-onset cases of diabetes in youth. Currently type 2 diabetes makes up 8-45% of new cases of diabetes in pediatric endocrinology clinics (Fagot-Campagna, Pettitt et al. 2000; Botero and Wolfsdorf 2005). If these trends continue, approximately one in three children who were born in the year 2000 will develop type 2 diabetes in their lifetime (Narayan, Boyle et al. 2003). Type 2 diabetes is not benign and is associated with a number of cardio-renal complications that significantly reduce life expectancy. Preliminary studies suggest that an earlier diagnosis carries a more dire prognosis, especially increasing the risk for renal complications (Pavkov, Bennett et al. 2006). Accordingly, strategies are urgently needed at the clinical as well as community level to identify and manage risk factors for type 2 diabetes in youth (Wei, Sung et al. 2003; Alberti, Zimmet et al. 2004). To develop effective approaches for the prevention and management of type 2 diabetes in youth, it is imperative to understand the modifiable risk factors that contribute to this diagnosis.

Data from adults demonstrate that type 2 diabetes can be prevented and managed through lifestyle changes, including increased habitual physical activity

(Tuomilehto 2001; Knowler, Barrett-Connor et al. 2002; Lindstrom, Ilanne-Parikka et al. 2006). This is especially relevant for youth, as the consequences of early development of type 2 diabetes and lifelong pharmacological management are not well understood. Data are beginning to emerge to support a relationship between physical activity and improved insulin sensitivity in youth (Bell, Watts et al. 2007; Kim, Im et al. 2007; McGavock, Sellers et al. 2007; Gill and Cooper 2008; van der Heijden, Wang et al.); however the required dose of physical activity and the mechanism of improved insulin sensitivity have not been well examined to date. We believe that there are three particular issues that, if addressed, could significantly reduce the burden of youth onset type 2 diabetes in Canada. These are:

1) **Physical activity for disease management:** What role does physical activity play in management of glycemia in youth diagnosed with type 2 diabetes?
2) **Physical activity as a biomarker**: Are youth with type 2 diabetes characterized by lower levels of physical activity and cardiorespiratory fitness compared to normoglycemic peers? and
3) **Physical activity for disease prevention**: Is high intensity physical activity superior to low intensity physical activity for the prevention of type 2 diabetes among overweight youth?

Chapter 2

Review of Literature

Pathogenesis of type 2 diabetes

Type 2 diabetes is a complex polygenic heritable disease, which is strongly influenced by several factors including dietary habits, physical activity, sedentary behaviour and obesity (Sullivan, Morrato et al. 2005; Morrato, Hill et al. 2007). Even in cases of type 2 diabetes that are highly attributable to single nucleotide genetic variants (Hegele, Cao et al. 1999; Lyssenko, Lupi et al. 2007), exposure to lifestyle factors including obesity and physical inactivity appear to accelerate the progression towards diabetes (Hegele, Zinman et al. 2003). It is therefore not surprising that the increased prevalence of type 2 diabetes in adults and youth parallels the dramatic increase in rates of obesity and declining levels of physical activity and fitness observed over the last three decades (Tremblay, Katzmarzyk et al. 2002; Tremblay and Willms 2003; Shields 2006). Accordingly, at presentation, youth with type 2 diabetes are typically overweight, report little habitual physical activity and show clinical signs of insulin resistance (Dean 1998; Alberti, Zimmet et al. 2004). As with adults, youth are also characterized by profound defects in insulin secretion in the absence of autoimmune antibodies suggestive of type 1 diabetes.

In the healthy state, blood glucose levels are tightly regulated by a balance between insulin secretion from beta-cells of the pancreas and insulin-mediated glucose disposal into metabolically active tissues (Figure 1). This balance between insulin secretion (or beta cell function) and glucose disposal (or insulin sensitivity) is termed the disposition index (Stumvoll, Goldstein et al. 2005). According to the parabolic association between these two factors, any decline in

peripheral insulin sensitivity such as that observed with obesity (Elder, Prigeon et al. 2006) is compensated for by an increase in insulin secretion (hyperinsulinemia) from beta cells to maintain normoglycemia. Failure to compensate for a prevailing reduction in insulin sensitivity leads to a loss of glycemic control (Elder, Prigeon et al. 2006), characterized by a downward and leftward shift in the disposition index and progression toward insulin resistance (Kobayashi, Amemiya et al. 2000; Gungor and Arslanian 2004). This metabolic decompensation is one of the first indicators of the progression to type 2 diabetes (Kobayashi, Amemiya et al. 2000). At the cellular level, a relative insulin secretory defect exists, as the pancreatic beta cells are failing to produce sufficient insulin for the prevailing level of insulin resistance and hyperglycemia ensues. At present, the environmental and biological mediators of this dysfunction remain poorly understood.

Tissue steatosis as a biomarker of type 2 diabetes

Several mechanisms have been proposed to explain the uncoupling of insulin secretion from insulin sensitivity including pancreatic amyloid accumulation, glucose toxicity, systemic inflammatory processes and lipotoxicity (Johnson, O'Brien et al. 1989; Unger 2003; Robertson, Harmon et al. 2004). Among these theories, the accumulation of lipid moieties within non-adipocytes *(termed steatosis)* is an attractive unifying hypothesis to explain the loss of glycemic control in youth onset type 2 diabetes (Corcoran, Lamon-Fava et al. 2007). Accordingly, steatosis may be one of the first biomarkers of type 2 diabetes in youth.

Under normal conditions, the lipid content within non-adipocytes serves as an immediate and efficient source of adenosine triphosphate (ATP) and levels are tightly regulated (Schick, Eismann et al. 1993). When these lipids accumulate and remain stagnant, as in the case of physical inactivity or impaired / decreased mitochondrial function, by-products such as ceramide and diacylglycerol can interfere with intracellular signalling, insulin receptor function and insulin clearance (Petersen, Dufour et al. 2004; Corcoran, Lamon-Fava et al. 2007; Kotronen, Vehkavaara et al. 2007). Collectively these factors can contribute to the pathological hyperinsulinemia characteristic of insulin resistance (Seppala-Lindroos, Vehkavaara et al. 2002).

Evidence for a causal association between steatosis and insulin sensitivity has been eloquently provided in adults through: (i) prolonged lipid infusion which substantially increases intramuscular triglycerides and induces insulin resistance (Bachmann, Dahl et al. 2001; Belfort, Mandarino et al. 2005), (ii) the enhancement of insulin sensitivity through medications that decrease intracellular lipid content (Teranishi, Ohara et al. 2007), and (iii) lifestyle interventions that reduce the burden of intracellular lipid and reduce insulin resistance in overweight individuals through enhanced mitochondrial oxidative capacity (Krssak and Roden 2004).

Indeed, there is convincing evidence in adults that ectopic lipid deposition and the resulting by-products play a major role in the natural history of type 2 diabetes (Krssak, Falk Petersen et al. 1999). It is reasonable to believe that these mechanisms also contribute to the progressive loss of glucose control in

youth.

One of the most clinically recognized forms of steatosis in youth, hepatic steatosis or *fatty liver disease,* is strongly associated with insulin resistance (Sagi, Reif et al. 2007). An inability to suppress hepatic glucose production in the face of hyperglycemia is one consequence of hepatic steatosis which can further exaggerate levels of glycemia (Samuel, Liu et al. 2004). Although fatty liver disease is present in up to 10% of the general pediatric population and approximately 40% of obese youth (Burgert, Taksali et al. 2006; Schwimmer, Deutsch et al. 2006; Angulo 2007), there has been limited study of the role of steatosis in youth onset type 2 diabetes, largely due to the invasiveness of tissue biopsy. With the advent of proton magnetic resonance spectroscopy (^{1}H-MRS) (Boesch, Slotboom et al. 1997; Szczepaniak, Babcock et al. 1999; Szczepaniak, Nurenberg et al. 2005) the opportunity now exists to accurately and non-invasively quantify levels of intracellular lipid in youth (Larson-Meyer, Newcomer et al. 2010). The few studies using this technology in youth have provided evidence to support the association between steatosis and insulin resistance in obese youth (Sinha, Dufour et al. 2002; Weiss, Dufour et al. 2003; Perseghin, Bonfanti et al. 2006) independent of subcutaneous fat (Sinha, Dufour et al. 2002), truncal adiposity and percent body fat (Perseghin, Bonfanti et al. 2006). Excessive intracellular lipid (or steatosis) may therefore serve as a “non-glycemic biomarker” for type 2 diabetes and be involved in the development of hyperinsulinemia that often accompanies obesity in youth (Koyama, Chen et al. 1997). Studies of intracellular lipid content in muscle and liver tissue of youth with

type 2 diabetes are needed to determine if steatosis is a feature of type 2 diabetes, and whether it is associated with modifiable lifestyle factors. This information would lead to the creation of a novel biomarker and lifestyle target for the prevention of type 2 diabetes in high risk youth.

Consequences of type 2 diabetes

It is critically important to prevent or delay the loss of glycemic control and progression to type 2 diabetes in youth. Early onset type 2 diabetes is associated with the presence of multiple cardiovascular risk factors including hypertension, dyslipidemia and microalbuminuria (McGavock 2007; Ruhayel, James et al. 2010). These co-morbid conditions likely contribute to the nearly five-fold increased rate of end-stage renal disease observed among patients with type 2 diabetes diagnosed during adolescence (Pavkov, Bennett et al. 2006).

A less appreciated consequence of type 2 diabetes is the dramatically increased risk of type 2 diabetes in the offspring of women diagnosed at an early age (Meigs, Cupples et al. 2000; Young, Martens et al. 2002). Among the Pima Indians who have the highest known prevalence of type 2 diabetes in the world, 70% of youth exposed to a diabetic intrauterine environment will be diagnosed with diabetes before the age of 35 (Dabelea, Knowler et al. 2000). Consequently, as more females develop diabetes in their childbearing years, more children are at risk for early diagnosis of type 2 diabetes and the age of diagnosis progressively becomes younger over the generations (Young, Martens et al. 2002; Hegele, Zinman et al. 2003). The ramifications of this vicious cycle of type 2 diabetes in more recent generations cannot yet be fully appreciated. It is clear

however that evidence based strategies to prevent and manage type 2 diabetes in youth are urgently required.

Management of type 2 diabetes in youth

As type 2 diabetes in youth is a relatively new phenomenon, clinicians have little empirical evidence on which to base treatment regimes. As such, clinical practice guidelines are largely based on expert consensus and data from research in adults (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008; Rosenbloom, Silverstein et al. 2008). The ultimate goal of treatment is to regain and maintain control of blood glucose levels, as glycemic control is a major determinant of diabetes-associated morbidity (Hanley, Harris et al. 2005; Pavkov, Bennett et al. 2006; Pinhas-Hamiel and Zeitler 2007). Clinically, glycemic control is determined by a measurement of glycosylated hemoglobin (HbA_{1c} %). Achieving an HbA_{1c} of ≤ 7% (i.e. target glycemic control) is recommended by experts as it is associated with a substantial reduction in complications (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008). Glycemic control may be targeted through changes in physical activity and nutrition alone (locally termed “lifestyle monotherapy”), or in combination with glucose lowering pharmacologic agents. This however, poses a unique challenge in pediatric cohorts as the long term consequences of glycemia lowering agents have yet to be determined. As such, lifestyle intervention is currently recommended as a front line treatment to achieve target glycemic control among youth with type 2 diabetes.

Research in adults diagnosed with type 2 diabetes demonstrates that changes in

physical activity and dietary practices not only prevent type 2 diabetes (Knowler et al, 2002) but also yield substantial improvements in glycemic control (Boule, Haddad et al. 2001; Pi-Sunyer, Blackburn et al. 2007; Sigal, Kenny et al. 2007). Importantly, the benefits of increased physical activity and dietary changes extend beyond glycemic control in both adults and youth, and positively affect blood pressure, blood lipids, albuminuria and other systemic and psychological conditions associated with type 2 diabetes (Pi-Sunyer, Blackburn et al. 2007; Janiszewski and Ross 2009; Johnson, Sachinwalla et al. 2009; Williamson, Rejeski et al. 2009; Janssen and Leblanc 2010).

Ideally, the management of type 2 diabetes and its complications in youth would be achieved with lifestyle changes alone. Not only do lifestyle changes elicit multiple cardiometabolic benefits but they also have limited long-term health-related side effects. In reality, clinical decisions and treatment paradigms are often based on a body of literature which suggests that only 6-12% of youth are able to achieve target control with lifestyle changes alone (McQuaid, O'Gorman et al. 2005; Peterson, Silverstein et al. 2007; Sheild, Lynn et al. 2009). While these studies suffer from major limitations, namely limited experience with small clinical cohorts or significant loss to follow-up, these data influence consensus-based treatment paradigms and early clinical use of drug therapy (Rosenbloom, Silverstein et al. 2008). Regrettably, there are no ongoing large-scale efforts to evaluate the use of lifestyle for the management of type 2 diabetes in youth (Gemmill, Brown et al. 2010). The TODAY study (Treatment Options for type 2 Diabetes in Adolescents and Youth) is a major ongoing randomized controlled

trial for the management of type 2 diabetes, however it does not include a lifestyle-only arm (Zeitler, Epstein et al. 2007). Further investigation is necessary to evaluate the efficacy of lifestyle therapy for the management of type 2 diabetes in youth.

Prevention of type 2 diabetes in youth

The premature development of risk factors for cardiovascular disease in youth-onset type 2 diabetes represents significant personal health risk and on a larger scale, forecasts a major burden on the healthcare system (King, Aubert et al. 1998; Wild, Roglic et al. 2004). Therefore, in addition to optimizing management of youth already diagnosed with type 2 diabetes it is imperative to focus on preventive efforts for youth at risk for type 2 diabetes. Studies indicate that physical activity is not only effective in managing levels of glycemia in adults with type 2 diabetes (Boule, Haddad et al. 2001; Sigal, Kenny et al. 2007), but that it is also an ideal tool to prevent the progression to type 2 diabetes in high risk individuals (Pan 1997; Knowler, Barrett-Connor et al. 2002; Lindstrom, Ilanne-Parikka et al. 2006). A similar body of knowledge does not currently exist for the prevention of type 2 diabetes in youth.

The effect of physical activity interventions on determinants of type 2 diabetes

Physical activity is an effective countermeasure against type 2 diabetes in adults. The Diabetes Prevention Program (DPP) provides compelling evidence for the effectiveness of increasing physical activity in the prevention of type 2 diabetes in high risk adults (Knowler, Barrett-Connor et al. 2002). Using a randomized controlled trial design, the DPP demonstrated that participation in a lifestyle

intervention designed to increase physical activity by 150 minutes per week reduced the incidence of type 2 diabetes by 58% compared with those randomized to a control group. These findings were similar to effects observed with randomized controlled trials in separate cohorts of adults with impaired glucose tolerance (IGT) from both Finland (Diabetes Prevention Study; DPS) (Tuomilehto 2001) and China (Da Qing Study) (Pan, Li et al. 1997). Impressively the benefits of lifestyle modifications in the DPS, DPP and Da Qing studies persisted for three, 10 and 14 years after the cessation of the respective active interventions (Lindstrom, Ilanne-Parikka et al. 2006; Li, Zhang et al. 2008; Knowler, Fowler et al. 2009). In contrast to this overwhelming evidence for the benefit of lifestyle intervention for the prevention of type 2 diabetes in adults, there is a surprising lack of evidence for the role of physical activity for the prevention of type 2 diabetes in youth.

Among the limited studies in youth, some of the most promising results are from physical activity interventions that have targeted increases in fitness levels. Several small trials in overweight youth have demonstrated reductions in fasting insulin levels with increased physical activity (Ferguson, Gutin et al. 1999; Carrel, Clark et al. 2005; Kim, Im et al. 2007) (Table 1). For example, overweight middle-school children randomized to a fitness based physical education course experienced a 10% increase in fitness and a corresponding 15% decrease in fasting insulin versus the control group that received a standard physical education curriculum (Carrel, Clark et al. 2005). A limited number of studies using more sensitive measures of insulin sensitivity have reported similar effects

with resistance training (Shaibi, Ball et al. 2006), combined diet and exercise programs (Monzavi, Dreimane et al. 2006; Savoye, Shaw et al. 2007) and higher intensity aerobic exercise training (Kang, Gutin et al. 2002; Shaibi, Cruz et al. 2006; Savoye, Shaw et al. 2007; van der Heijden, Wang et al. 2010). Only one identified study to date has evaluated the effects of a structured aerobic program (combined with resistance training) using direct measures of insulin sensitivity in a small sample of obese youth (Bell, Watts et al. 2007). Bell and colleagues found an 18% increase in insulin sensitivity after a mere eight weeks of resistance (55-65% voluntary contraction) and aerobic activities (65-85% HR max) performed for one hour, three times per week.

Only one study was identified that was specifically designed to compare changes in insulin sensitivity between groups of children assigned to low versus high intensity exercise (Kang, Gutin et al. 2002). Kang and colleagues randomised 80 youth to receive lifestyle education (LSE) and low intensity exercise (55-60% VO_{2peak}), LSE and high intensity exercise (75-80% VO_{2peak}) or a control condition of LSE alone (Kang, Gutin et al. 2002). After eight months within their respective allocations only 17 youth randomized to either exercise group attended ≥40% of the sessions and achieved the recommended training dose. While fasting insulin levels tended to improve the most in the high intensity exercise arm, this was not significant likely due to the low rates of adherence to exercise intensity and consequently a lack of statistical power. Subsequently, the exercise groups were combined into one for analysis versus the control group. Therefore, the appropriate dose of physical activity required to elicit an improvement in insulin

sensitivity in youth remains unclear.

Mechanism of improved insulin sensitivity with moderate intensity physical activity

While the precise mechanism for improved blood glucose control with physical activity is not known, the activation of 5'AMP-activated protein kinase (AMPK) plays a pivotal role (Fujii, Hayashi et al. 2000; Nakano, Hamada et al. 2006). AMPK is a heterotrimeric enzyme that functions as an intracellular fuel gauge, which is activated upon decreases in ATP such as that seen with muscular contraction (Hardie, Salt et al. 1999). The downstream effects of AMPK activation are an increase in ATP production and restoration of the energy charge of the cell. Specifically, AMPK increases glucose uptake by inducing translocation of skeletal muscle glucose receptors (GLUT-4) (Kurth-Kraczek, Hirshman et al. 1999), enhances fatty acid uptake through promotion of CD36 translocation (Kelly, Abbott et al. 2010) and increases fat oxidation through inhibition of malonyl-CoA (Merrill, Kurth et al. 1997). The direct enhancement of glucose uptake and utilization of intracellular lipid stores may be the pivotal link between exercise and enhanced insulin sensitivity. AMPK may also exert its effects indirectly through the hypothalamus, as well as by mediating the leptin, adiponectin, PGC1α and inflammatory pathways (Towler and Hardie 2007).

Importantly, AMPK is preferentially activated by moderate to high intensity physical activity (≥ 70% of VO_{2max}) rendering lower intensity physical activity less effective for improving insulin sensitivity (Fujii, Hayashi et al. 2000; Wojtaszewski, Nielsen et al. 2000; Stephens, Chen et al. 2002). In addition to directly increasing

glucose uptake, AMPK activation may enhance insulin sensitivity by reducing intracellular lipid content secondary to increased fat oxidation. Accordingly, higher intensity exercise may have the potential to reverse altered lipid partitioning and reduce tissue steatosis. Therefore, physical activity at or above 70% of VO_{2max} may be the preferred stimulus to prevent type 2 diabetes through AMPK-mediated increases in glucose uptake and fat oxidation and subsequent reductions in intracellular lipid content (Figure 2). Importantly, the AMPK signaling pathway is preserved in both animal models and adults with type 2 diabetes (Musi, Fujii et al. 2001; Sriwijitkamol, Ivy et al. 2006). It therefore represents a vital therapeutic lifestyle target for enhancing insulin sensitivity, reducing tissue steatosis and achieving optimal glycemic control in the face of obesity and beta cell defects. The association between exercise intensity, AMPK activity, steatosis and insulin sensitivity has important implications for the prevention and clinical management of type 2 diabetes.

Interventions designed to capitalize on the relationship between exercise intensity, AMPK activation and intracellular lipid could inform clinical approaches to the management of insulin resistance in youth. While there is ample biological evidence for the role of higher intensity exercise for improving insulin sensitivity in youth, very few studies exist testing the dose-response association between exercise intensity and insulin sensitivity in overweight youth.

Questions that remain

In conclusion, while it is generally accepted that physical activity is associated with health benefits among youth, several key questions remain unanswered that

carry significant clinical and policy relevance: First; ‘Can youth with new-onset type 2 diabetes successfully use lifestyle therapy to achieve and maintain target glycemic control?’ Second; ‘Are youth with type 2 diabetes characterized by low levels of fitness and physical activity, and is this associated with tissue steatosis?’; and finally; ‘Is high intensity physical activity superior to low intensity physical activity to improve insulin sensitivity and reduce tissue steatosis in youth at risk for diabetes?’ The purpose of this thesis is to provide preliminary evidence to answer these pressing questions and provide much needed empirical evidence for the role of physical activity in the prediction, prevention and treatment of type 2 diabetes among youth.

Purpose

This thesis is comprised of three studies that examine the role of physical activity and cardiorespiratory fitness across the natural history of type 2 diabetes in youth ages 13-18 years.

Study A.

Success with Lifestyle Monotherapy in Youth with New-Onset Type 2 Diabetes

Research Question: 'Can youth with new-onset type 2 diabetes successfully use lifestyle therapy to achieve and maintain target glycemic control?'

A mixed methods retrospective chart review was designed to inform current practice guidelines, which are largely based on expert consensus. The purpose was to describe 10 years of clinical experience with lifestyle monotherapy for the successful management of hyperglycemia in youth with type 2 diabetes in Winnipeg Manitoba. **The primary hypothesis is that within youth with type 2 diabetes who are eligible for lifestyle intervention at diagnosis (i.e. HbA_{1c} < 9.0%) a clinically significant proportion can achieve target glycemia with lifestyle changes alone.**

Study B.

Physical Activity, Cardiorespiratory Fitness, Intrahepatic Lipid and Glucose Tolerance in Adolescents

Research Question: Are youth with type 2 diabetes characterized by low levels of fitness and physical activity, and is this associated with tissue steatosis?

Low physical activity and cardiorespiratory fitness are associated with a clustering of risk factors for type 2 diabetes and serve as robust predictors of the

transition from normoglycemia to glucose intolerance in overweight adults (LaMonte, Barlow et al. 2005). In youth, the value of fitness as a modifiable biomarker for type 2 diabetes remains unclear (McGavock, Sellers et al. 2007). **In this context, a cross-sectional study was designed to test the hypothesis that youth with type 2 diabetes are characterized by low physical activity and low cardiorespiratory fitness levels. Furthermore we hypothesized that both physical activity and fitness levels are associated with conventional and novel risk factors for type 2 diabetes in youth.**

Study C.

The POWER Trial: Interim analysis

Research Question: Is high intensity physical activity superior to low intensity physical activity to improve insulin sensitivity and reduce tissue steatosis?

The POWER Trial (Physical activity for OverWEight youth at Risk for diabetes) is a multi-arm randomized controlled trial comparing the effects of different physical activity intensities on insulin sensitivity and risk factors for type 2 diabetes in overweight youth. **This trial is specifically designed to test the hypothesis that high intensity physical activity (70-85% of heart rate reserve) is superior to low intensity activity (40-55% of heart rate reserve) for improving risk factors for type 2 diabetes in overweight youth. Specifically, high intensity activity will be more effective for improving insulin sensitivity and reducing tissue lipid content in overweight youth at risk for type 2 diabetes.** This interim analysis will present trends observed in the first third of the trial.

Table 1. Physical activity interventions designed to improve whole body insulin sensitivity in youth

Reference	*N (intervention)* *Sex (m/f)*	*age*	*Control (y/n) Details*	*Exercise*			*Outcome*	
				Frequency /mode	*Intensity*	*Duration*	*Insulin sensitivity (Si) measure*	*% change**
van der Heijden et al, 2010 (van der Heijden, Wang et al. 2010)	29 (15 obese / 14 lean)** 7/8	Obese 15.6±.04 Lean 15.1±0.1	Y Lean youth receiving interv.	4 d/wk, aerobic 2d/wk supervised, 2d/wk alone	≥70% HRmax (>140 bpm)	30min (plus 10 min warm up, 10 min cool down) 12 weeks	HOMA-IR I_F , G_F	16.5% ↓ I_F 16% ↓ in HOMA
van der Heijden et al, 2010 (van der Heijden, Wang et al. 2010)	12 6/6	15.5±0.5	N	2 d/wk Strength training	Progressive increase from 50%RM_{max} to 85%RM_{max}	60 min/session 12 weeks	Stable labeled IVGTT	NS (whole body Si) (24%↑in hepatic Si)
Elloumi et al 2009 (Elloumi, Ben Ounis et al. 2009)	7 7/0	13.1±0.7	Y Energy restriction (RE; n=7) or RE and exercise (n=7)	4 d/wk Running, jumping, ball games	HR of maximal rate of lipid oxidation†	90 min/session 2 months	HOMA-IR	37.7% ↓ I_F 35.7% ↓ in HOMA-IR
Farpour-Lambert et al 2009 (Farpour-Lambert, Aggoun et al. 2009)	22 9/13	8.9±1.5	Y Inactive controls; modified cross over design§	2-3 d/wk§ 30min aerobic, 30 strength & stretch	Between 55-65% VO_{2max}	60 min/session 6 months	HOMA-IR I_F , G_F	NS change at 3 months 0.96 ↓ HOMA-IR at 6 months¶
Tsang et al 2009 (Tsang, Kohn et al. 2009)	12 5/7	13.1±2.1	Y Tai chi	3 d/wk Kung-Fu	Not specified	60 min/session 6 months	HOMA-IR I_F , G_F	NS

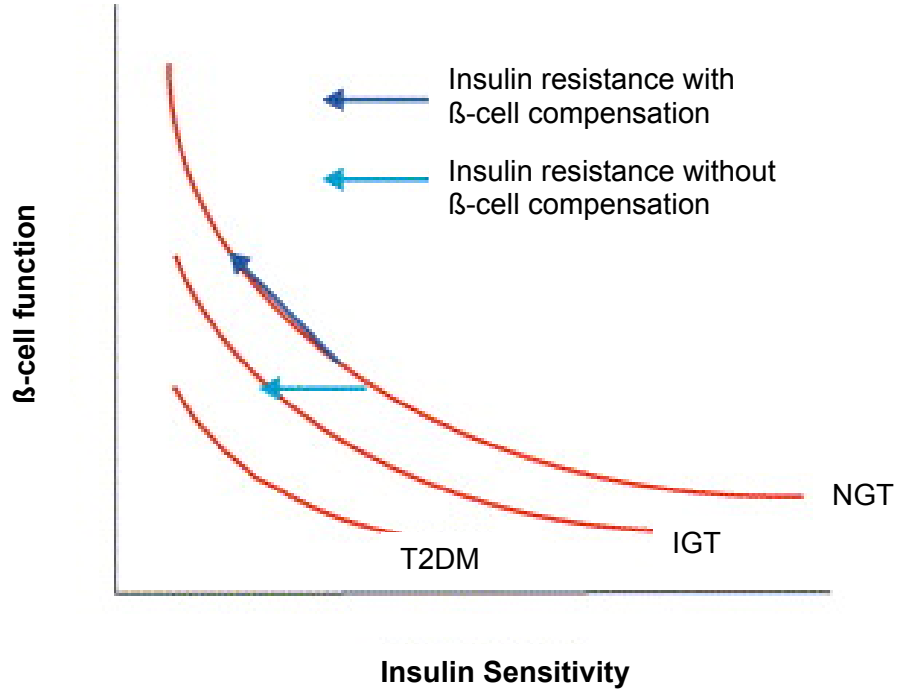
Reference (Table 1 continued)	*N (intervention) Males/females*	*Age (years)*	*Control (y/n) Details*	*Exercise*			*Outcome*	
				Frequency /mode	*Intensity*	*Duration*	*Si measure*	*% change*
Chang et al, 2008 (Chang, Liu et al. 2008)	33 25/8	12-14	Y regular phys-ed (n=32)	month 0-3: 7d/wk month 4-9: 6d/wk aerobic & strength	145-160bpm 5-7 METS	month 0-3: 60-90 min month 4-9: 15-40 min	HOMA-IR I_F , G_F	HOMA-IR ↓ 48.5% I_F ↓ 36.6% G_F↓ 23.1%
Kelishadi et al, 2008[¥] (Kelishadi, Hashemipour et al. 2008)	45 Sex ratio not specified	7-9	Y Hypocaloric diet n= 47	5 d/wk Fitness oriented activities, games, running	Not specified	40 min aerobic activities 15 min education 6 months	HOMA-IR QUICKI	NS
Kim et al 2007 (Kim, Im et al. 2007)	14 14/0	17±0.11	Y Regular phys-ed 12 obese 14 lean	5 d/wk Jump rope	Progressed by increasing jumps per minute and reducing rest	40min/session 6 weeks	HOMA-IR I_F , G_F	31.5% ↓ I_F 33.6% ↓ in HOMA-IR
Bell et al, 2007 (Bell, Watts et al. 2007)	14 8/6	9-16	N	3 d/wk, aerobic and resistance circuit	Progressive, 55-65% voluntary contraction, 65-85% HRmax	1 hour/session 8 weeks	Euglycemic-hyperinsulinemic clamp	22% ↑ insulin sensitivity
Shaibi et al, 2006 (Shaibi, Cruz et al. 2006)	11 11/0	15.1±0.5	Y No exercise (n=11)	2 d/wk resistance training	Progressive and periodized	<1 hr/session 4 months	FSIVGTT I_F	39% ↑ insulin sensitivity 10%↓ I_F

Reference (Table 1 continued)	*N (intervention) Males/females*	*age*	*Control (y/n) Details*	*Exercise*			*Outcome*	
				Frequency /mode	*Intensity*	*Duration*	*Si measure*	*% change*
Nassis et al, 2005 (Nassis, Papantakou et al. 2005)	21 0/21	9-15	N	3 d/wk, group based aerobic activity	HR >150bpm	40 min/session 12 weeks	<u>OGTT:</u> Insulin AUC HOMA-IR	23.3% ↓ insulin AUC ∆HOMA NS
Carrel et al, 2005 (Carrel, Clark et al. 2005)	50 26/ 24	12±0.5	Y Regular gym class (n=35-40)	5d/2 wks fitness-based gym class, smaller classes (n=12-14)	Not specified	45 min/session 9 months	I_F , G_F	14.8% ↓ fasting insulin
Kang et al, 2002 (Kang, Gutin et al. 2002)	41 Sex ratio not specified	13-16	Y Lifestyle education	5 d/wk 250 kcal/session, individualized program based on treadmill test	Low intensity @ 55-60% peak VO2 High intensity @ 75-80% peak VO2	30-45 min/session 8 months	I_F , G_F	NS[£]
Ferguson et el, 1999 (Ferguson, Gutin et al. 1999)	79 26/53	7-11	Y Cross-over design	5 d/wk 20 min on aerobic machines, 20 min aerobic games	Average HR during training 157 bpm	40 min/session 4 months	I_F , G_F	9.5-20.3% ↓ I_F
Kahle et al, 1996 (Kahle, Zipf et al. 1996)	7 7/0	11-14	N	3 d/wk calisthenics, walking, jogging, jump rope, games	60-70% predicted max HR	Progressive from 20min to 40min 15 weeks	Response to a mixed meal I_F , G_F Peak glucose, Peak insulin	Significant ↓ glucose & insulin (peak values and AUC); ↓G_F

Table 1 Abbreviations and Symbols

AIR (acute insulin response)
AUC (area under the curve)
bpm (beats per minute)
FSIVGTT (frequently sampled intravenous glucose tolerance test)
G_F (fasting glucose)
HOMA-IR (homeostasis model of insulin resistance)
HR (heart rate)
HRmax (maximal heart rate)
I_F (fasting insulin)
OGTT (oral glucose tolerance test)
QUICKI (quantitative insulin sensitivity check index), $1/[\log(I_F) + \log(G_F \text{ in mg/dL}]$
RM_{max} (1 repetition max)
Symbols:
* % change in insulin sensitivity measure provided when pre and post data available, otherwise change denoted in format provided in manuscript.
** results presented for obese participants only
† exercise intensity that corresponds to maximal rate of lipid oxidation.
§ 22 youth received 6months of intervention (3x/wk for first 3 months and 2x/wk for remaining 3months), 22 controls joined the intervention group at 3months and participated in the 3x/wk program)
¶ Data was only analyzed for those completing the intervention at 6 months (n=18/22)
¥ Study was designed to test change in ghrelin as primary outcome
£ Trend for significance at p=0.085 between intervention and control

Figure 1: Hyperbolic relation between beta-cell function and insulin sensitivity.



In people with normal glucose tolerance (NGT) a quasi-hyperbolic relation exists between beta-cell function and insulin sensitivity. With deviation from this hyperbola, deterioration of glucose tolerance (impaired glucose tolerance [IGT], and type 2 diabetes [T2DM]) occurs.

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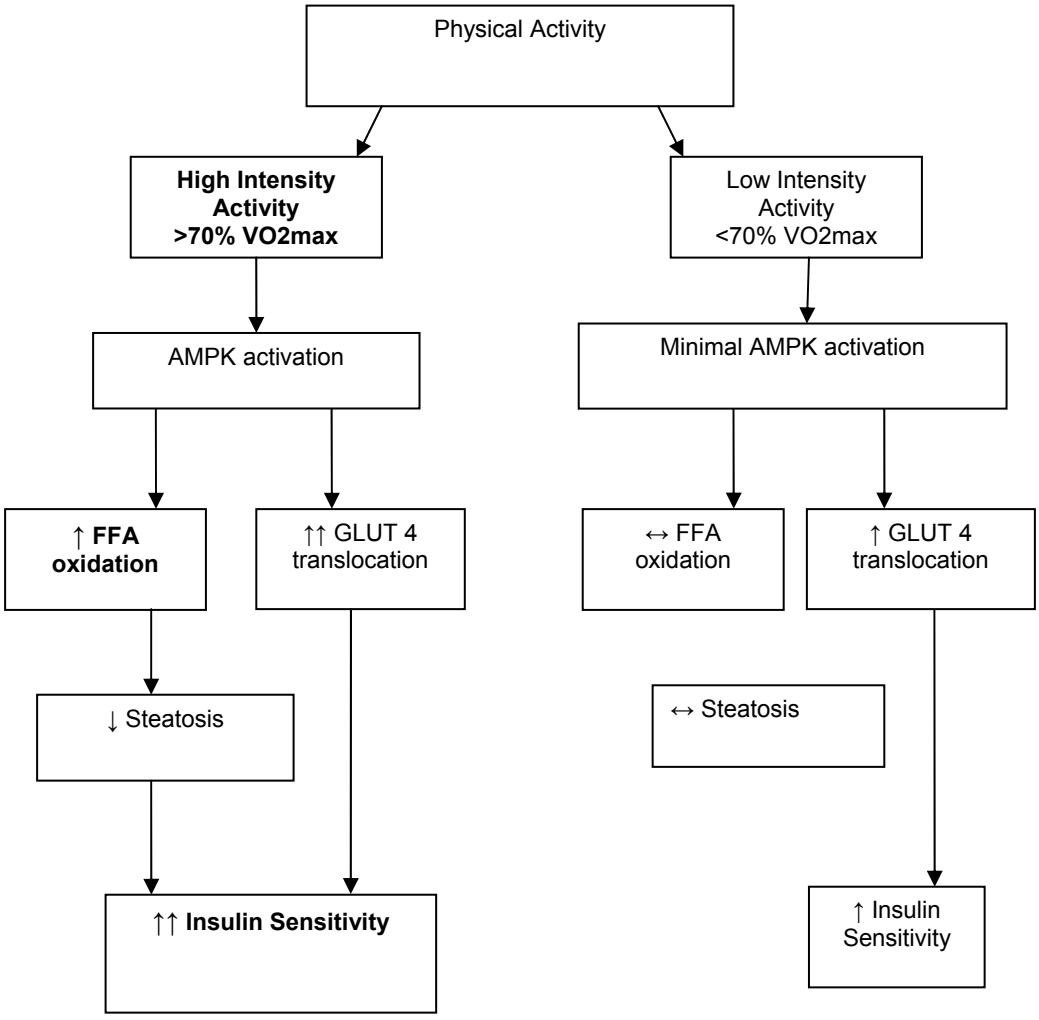
Figure 2: Proposed acute mechanisms leading to superior improvement in insulin sensitivity with high intensity versus low intensity exercise through actions of AMPK.

The activation of AMPK at or above moderate intensity is associated with increases in free fatty acid (FFA) oxidation and subsequent reductions in steatosis; providing additional mechanisms by which to improve insulin sensitivity.



Chapter 3

Study A.

Success with Lifestyle Monotherapy in Youth with New-Onset Type 2 Diabetes

RATIONALE

Evidence is lacking to show the effect of lifestyle modification as first line therapy in the clinical management of type 2 diabetes in adolescents. This study describes the success rate and factors associated with achieving target glycemic control with non-pharmacologic management (herein referred to as *lifestyle monotherapy)* in the year following diagnosis in a large clinical cohort of youth with type 2 diabetes.

METHODS

Study design and population: This was a retrospective chart review of youth with type 2 diabetes treated at a pediatric endocrinology clinic, combined with a semi-quantitative lifestyle survey. Charts of youth (< 18 years of age) with type 2 diabetes treated at the Diabetes Education Resource for Children and Adolescents (DERCA) in Winnipeg Manitoba between 1999 and 2008 were screened to identify those treated with lifestyle monotherapy at diagnosis. The DERCA is the only specialized pediatric diabetes program providing services to a population of 1.5 million people living in Manitoba and northwestern Ontario. Youth treated at this centre were seen by a pediatric endocrinologist, a dietitian, and a nurse educator three to four times annually. In 2007 an exercise specialist was added to the team. At diagnosis and each subsequent visit, all youth receive lifestyle education from this team on strategies to improve nutritional habits, increase physical activity and reduce sedentary / screen time.

Medical charts were reviewed for patients diagnosed with type 2 diabetes between January 1st 1999 and January 1st 2008 who had at least one year of follow-up in the clinic. The diagnosis of type 2 diabetes was made using the criteria published by the American and Canadian Diabetes Associations (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008; American Diabetes Association 2009).

A flow chart describing the inclusion criteria is provided in Figure A 1. Of the 275 potential charts available to review, 189 were excluded because (1) patients were in significant metabolic decompensation at diagnosis (i.e. HbA_{1c} ≥ 9% and/or diabetic ketoacidosis) and required insulin (n=157), (2) charts did not contain HbA_{1c} data as diagnosis was in a remote location (n=8), or (3) patients did not have complete data at one year following diagnosis (n=24). In total, charts from 86 youth (51 females and 35 males) met inclusion criteria and had sufficient follow-up data to be included in the analysis. Youth were classified as having 'incomplete follow-up' if they were lost to follow-up, transferred to adult care within 12 months of diagnosis or did not have a clinic visit between 11 and 16 months after diagnosis (n=24).

Protocol and data extraction: The 86 eligible charts were subdivided into two groups based on HbA_{1c} levels 12 months after diagnosis; (1) patients who achieved and maintained target HbA_{1c} of ≤ 7.0% as defined by Canadian Diabetes Association and ISPAD Guidelines (Canadian Diabetes Association

Clinical Practice Guidelines Expert Committee 2008; Rosenbloom, Silverstein et al. 2009) and (2) those who did not achieve or maintain target glycemic control at 12 months, or required pharmacological support to achieve target control. HbA_{1c} measurements were obtained at clinic visits every four to six months. All charts included in the final analysis had a minimum of two follow-up measurements. Demographic data including age, gender and ethnicity (self-defined as First Nations, Caucasian or other) were extracted from charts, as well as anthropometric data including weight, height, BMI z-score and blood pressure. Laboratory data extracted from the charts included $HbA_{1c,}$ total cholesterol, LDL, HDL, triglycerides and liver enzymes (ALT, AST). Fasting insulin, fasting glucose, apolipoprotein B, albumin-creatinine ratio (ACR) and HNF-1α G319S genotype were recorded when available. HNF-1α G319S is a polymorphism unique to the Oji-Cree population from northeastern Manitoba and northwestern Ontario and is associated with early onset type 2 diabetes (Sellers, Triggs-Raine et al. 2002).

Following the chart review, a research assistant contacted eligible participants and administered a questionnaire regarding physical activity, sedentary time and nutrition behaviours. Survey questions were based on the previously validated World Health Organization *Health Behaviours of School-Age Children Survey (HBSC)* questions, and included revisions made for the 2001-02 HBSC Survey (Prochaska, Sallis et al. 2001; Currie, Roberts et al. 2004; Iannotti, Kogan et al. 2009). In addition to lifestyle behaviours, information was collected regarding the

perceived barriers and difficulties with lifestyle change. Participation in the survey was limited to youth still attending the DERCA and therefore did not include those already transferred to adult care. Completion of the survey over the telephone was offered to youth who missed clinical visits over the period of data collection. Informed consent was obtained from all youth who participated in the questionnaire portion of the study and their guardians. The study protocol was approved by the Human Research Ethics Review Committee, Faculty of Medicine of the University of Manitoba in accordance with the Declaration of Helsinki.

Statistical Analysis: Clinic Data

Quantitative data are expressed as mean ± standard deviation. Student's t-test was used to test for group-wise differences in continuous characteristics and a chi squared test was used to test for differences in categorical variables. Repeated measures analysis of variance (ANOVA) was performed to test for group wise differences in the change over one year for each of the outcome variables listed in Table 2. As the BMI z-score data were not normally distributed, the Mann-Whitney U test for independent means was performed to test for between group differences. Multiple linear logistic regression was used to test which variables were independently associated with success. A p value < 0.05 was considered significant. All statistical analyses were performed using SPSS© statistical software (Version 16.0, Release 10.0.1, SPSS Inc, Chicago Illinois).

Physical Activity and Nutrition Questionnaire

Questionnaire data were analyzed by grouping categorical variables and reporting the percentage of respondents within each category. The average physical activity level was categorized as follows: inactive (≥ 60 minutes of activity on less than 2 days/week), moderately active (≥ 60 minutes of activity on 3-4 days/week) and active (≥ 60 minutes of activity on 5-7 days/week), corresponding with recent evidence based physical activity recommendations for this age group (Strong, Malina et al. 2005). Sedentary activities included screen time (TV watching, computer use, video games etc.), as well as time spent on homework. Sedentary time was categorized as low (0-2 hours/day), moderate (3-4 hours/day) or high (≥ 5 hours/day). Dietary behaviours were categorized based on frequency of meals or specific foods consumed (days / week).

RESULTS

Characteristics of each group at diagnosis are presented in Table A 1 and Table A 2. Among the 86 youth included, 52% (n=45) maintained an HbA_{1c} ≤ 7.0% during a period of 12 months with lifestyle therapy alone. This group of patients was characterized by a lower mean HbA_{1c} ($p<0.001$) and higher fasting insulin levels at diagnosis ($p=0.05$). There were no differences in age, ethnicity, HNF1α G319S genotype, BMI z-score, blood pressure z-score or other biochemical measures at diagnosis between youth who were successful or unsuccessful with lifestyle monotherapy.

Youth who were excluded from the study due to incomplete follow-up data (n=24) presented with an HbA_{1c} of 7.0±0.9%. At baseline, these youth did not differ significantly from youth included in the study with the exception of age (13.4±2.7 vs. 12.2±2.2 years, p=0.02, data not shown).

Characteristics of youth at one year following diagnosis are presented in Table A 2. As per the study design, the change in HbA_{1c} was significantly different between the groups at one-year follow-up (-0.7±1.0 vs. +1.7±2.2%, p<0.001). Accordingly, fasting blood glucose values increased significantly in the unsuccessful group compared to the successful group over the 12-month follow-up period. While BMI z-score decreased in both groups, this change was only significant in the unsuccessful group (p=0.07 for successful group). Finally, albumin / creatinine ratio increased in the unsuccessful group (p=0.05) at one year and decreased in the successful group (non-significant) at one year following diagnosis. No differences were noted in other recorded co-morbidities between the groups at follow-up.

Results from the questionnaires are presented in Table A 3 and Table A 4. Of the 86 charts reviewed for the study, 28 youth agreed to complete the questionnaire (17 successful with lifestyle monotherapy and 11 unsuccessful with lifestyle monotherapy). There were no statistical differences in the responses to survey questions between groups. Accordingly, the number of youth stating that their current level of physical activity had increased significantly since being

diagnosed with type 2 diabetes was similar between the two groups (proportion of youth in each group; 65% successful vs. 73% unsuccessful). Although non-significant, the number of youth reporting that they perform ≥ 60 minutes of physical activity on more than 4 days in a typical week was higher in the successful group relative to their unsuccessful counterparts (59% vs. 45% respectively). Seventy-six percent of youth in the successful group reported decreasing their consumption of sugar-containing drinks following their diagnosis of type 2 diabetes versus 54% in the unsuccessful group (NS).

When successful youth were asked through an open-response question what they considered the most important factor for achieving optimal glycemic control, 6% reported family support, 38% reported increased physical activity, 25% reported better nutrition and 25% reported both increased physical activity and better nutrition. Subsequently, when asked whether physical activity or nutrition has been the hardest to change since being diagnosed with type 2 diabetes, 50% reported nutrition as the hardest to change, while 19% reported that physical activity was the most difficult behaviour change.

DISCUSSION

This retrospective chart review, from the largest clinical pediatric cohort of youth with type 2 diabetes in Canada (Amed, Dean et al.), revealed several novel observations relevant to the management of glycemic control. First, optimal glycemic control with lifestyle monotherapy was achieved for one year following

diagnosis in more than 50% of our patients presenting with an HbA_{1c} < 9%; a substantially larger proportion of youth than has previously been reported. Second, among the clinical variables documented at diagnosis, only lower HbA_{1c} and higher fasting insulin levels appeared to be related to achieving long-term glycemic control with lifestyle monotherapy. These data suggest that lifestyle interventions may be more effective for youth diagnosed at an earlier stage of metabolic decompensation. Finally, youth with type 2 diabetes perceive physical activity to be an important and realistic modifiable lifestyle factor associated with achieving target glycemic control. Notably, success with lifestyle therapy was independent of changes in BMI z-score and did not require intensive lifestyle intervention beyond standard clinical care. Taken together, these data suggest that lifestyle monotherapy is a clinical option for achieving glycemic control in youth diagnosed with type 2 diabetes who do not present in metabolic decompensation.

Amidst a lack of empirical evidence for strategies to achieve glycemic control in youth with type 2 diabetes, the current study provides insight into our clinical experience with lifestyle monotherapy (McGavock 2007; Pinhas-Hamiel and Zeitler 2007). Intervention studies clearly demonstrate that increasing physical activity significantly improves glycemic control in adults with type 2 diabetes (Boule, Haddad et al. 2001; Sigal, Kenny et al. 2007). Among the limited intervention studies in youth, including the ongoing TODAY trial (Zeitler, Epstein

et al. 2007), none have included an arm of lifestyle change alone. The current data provide evidence to include a lifestyle modification only arm in any treatment trial and support further research into the role of lifestyle modification alone for the management of youth with type 2 diabetes with HbA_{1c} < 9%.

Our findings contradict previous studies of smaller cohorts of youth with type 2 diabetes in which only ~10% were able to achieve target glycemic control with lifestyle therapy alone (Grinstein, Muzumdar et al. 2003; Reinehr, Schober et al. 2008; Sheild, Lynn et al. 2009). Several factors likely explain the discrepancy between our findings and others. First, we excluded charts from youth presenting with metabolic decompensation at diagnosis (HbA_{1c} ≥ 9%) while others did not (Grinstein, Muzumdar et al. 2003). Nonetheless, if we had included these youth in the analysis, 19% (45/243) were successful with lifestyle alone after one year. Second, the emphasis and time spent on lifestyle education is a critical determinant of behaviour change among patients with type 2 diabetes. Unfortunately this was not documented in a manner in which it could be measured in our study, nor was it reported in previous reports. Consequently, we were also unable to assess adherence to specific components of the lifestyle education, or the effect of having an exercise specialist join the clinic in 2007. The details of lifestyle counseling are a potentially important difference between studies that could explain disparate success rates with lifestyle therapy. Details of clinical management should be carefully examined in future research. Third,

while other studies reported significant loss to follow-up (>50%), less than 10% of the charts we reviewed for this study were missing follow-up data at 12 months. Finally, as type 2 diabetes is more common in our catchment area, it is likely that youth were detected earlier and were likely at an earlier stage of metabolic decompensation. In line with this theory, our data suggest that youth diagnosed at more mild stages of dysglycemia (i.e. a lower HbA_{1c} and higher fasting insulin at diagnosis) are most amenable to lifestyle treatment; however future research is required to address this theory.

Consistent with observational studies of obese youth (Taveras, Berkey et al. 2005; Ekelund, Brage et al. 2006), increased physical activity, decreased screen time, increased fruit and vegetable consumption and decreased consumption of sweets and sugar-containing drinks appear to be predictors of successful management of glycemic control. Although self-reported, these observations provide important practical information for health care practitioners working with youth with type 2 diabetes.

Limitations: Data for this study were collected retrospectively from patient charts and therefore are susceptible to information bias and missing data. Factors unrelated to those recorded in clinical charts may additionally influence successful management of glycemia, in particular socioeconomic status. Similarly, pubertal stage was not consistently reported in the charts and as such could not be abstracted. Youth in the successful and unsuccessful groups were

the same mean age at diagnosis; however a wide age range (~7-17 years) at diagnosis within both groups may have impacted the results. With respect to questionnaire data, while proportions of successful and unsuccessful individuals appeared to differ in physical activity and nutrition habits, we were insufficiently powered to detect significant differences. This may have been compounded by a source of error inherent to the use of questionnaires. While there was no significant difference in the proportion of First Nations youth in the two groups (successful and unsuccessful), the large representation of First Nations youth within this cohort limits generalization of the findings. Further, as the HNF1α variant is restricted to youth of Oji-Cree heritage within communities in Northeastern Manitoba and Northwestern Ontario (Hegele, Zinman et al. 2003), only youth from those communities are screened for HNF1α status, limiting our power to perform sub-group analyses.

Optimal glycemic control for up to one year is possible with lifestyle monotherapy in youth with type 2 diabetes presenting with an HbA_{1c} < 9% at diagnosis, independent of changes in BMI z-score. These improvements in glycemic control were made following regular education and counseling during outpatient clinic visits. It is possible that higher rates of success with lifestyle monotherapy may be realized with a more intensive lifestyle program similar to that provided in the Diabetes Prevention Project and Look Ahead Trial (Wadden, West et al. 2006; Zeitler, Epstein et al. 2007). In light of the large proportion of youth successful

with lifestyle monotherapy, randomized control trials of non-pharmacologic treatment options for achieving glycemic control in youth with type 2 diabetes are warranted. This study provides data to inform the design of these trials and evidence that careful attention to lifestyle modification is an important clinical target for the management of youth with type 2 diabetes.

Tables Study A.

Table A 1. Baseline characteristics and anthropometrics of patients categorized by success with lifestyle management.

Baseline	**Successful ($HbA_{1c} \leq 7\%$ for 1 year)**	**Unsuccessful ($HbA_{1c} > 7\%$ for 1 year)**
N	45	41
Age at diagnosis mean (range)	13.0 (6.8-16.5)	12.4 (7.0-17.0)
Male	23 (51%)	13 (32%)
Ethnicity (FN/C/Other)	38/4/3	38/1/2
HNF-1α genotype (GG/GS/SS/not available)	13/3/9/20	15/8/9/9

FN: First Nation
CS: Caucasian
HNF1α; Hepatic Nuclear factor 1 alpha; GG (wildtype), GS (heterozygote), SS (homozygote).

Table A 2. Baseline and 1 year characteristics of sample.

Variable	Successful		Unsuccessful		Between groups p value	
	Baseline	1 year	Baseline	1 year	Baseline	Δ over 1 year
BMI z score	2.1 (0.7)	2.0 (0.7)	2.0 (0.7)	1.8 (0.8)†	0.37	0.34
SBP z score	1.6 (1.3)	1.3 (1.1)	1.2 (1.2)	1.2 (1.4)	0.16	0.49
DBP z score	0.7 (0.6)	0.5 (0.8)	0.9 (0.7)	0.5 (0.8)	0.36	0.29
HbA_{1c}	6.8 (1.0)*	6.1 (0.6)†	7.3 (0.7)*	9.0 (2.0)†	0.006	<0.001**
ACR‡	14.9 (45.2)	6.4 (21.5)	1.8 (2.0)	4.8 (10.1)	0.12	0.28
Chol‡	4.4 (0.9)	4.2 (0.9)	4.5 (0.9)	4.4 (1.0)	0.51	0.97
HDL‡	1.2 (0.2)	1.3 (0.7)	1.3 (0.3)	1.3 (0.2)	0.30	-
LDL‡	2.5 (0.7)	2.3 (0.6)	2.4 (0.5)	2.4 (0.6)	0.63	-
TG‡	1.7 (0.8)	1.8 (1.2)	1.7 (0.7)	2.0 (1.5)	0.86	0.64
ApoB‡	1.8 (4.2)	2.2 (5.7)	3.9 (12.3)	0.8 (0.3)	0.52	-
ALT‡	58 (51)	44 (37)	76.1 (75.2)	87.1 (90.6)	0.39	0.50
AST‡	38 (31)	38 (33)	49.4 (36.4)	59.5 (48.4)	0.31	0.36
I_f‡	323.1 (222.8)*	178.2 (170.7)	199.8 (161.3)*	187.6 (204.1)	0.05	-
G_f‡	7.0 (2.3)	6.3 (1.3)	8.2 (2.9)	10.9 (4.6)	0.06	<0.001**

* significant difference between groups at baseline ($p<0.05$)
**significant difference between groups for change over 1 year ($p<0.05$)
†significant change within group over 1 year ($p<0.05$)
Note: Change in the following variables not reported as there were <10 cases with pre and post data: insulin, HDL, LDL, Apo B.
‡ Missing laboratory data. N sizes as follows: ACR: baseline n=62 (33 successful), 1 year n=68 (33 successful)
Cholesterol: baseline n=68 (35 successful), 1 year n=51 (23 successful)
HDL: baseline n=21 (14 successful), 1 year n=24 (14 successful)
LDL: baseline n=41 (23 successful), 1 year n=30 (18 successful)
TG: baseline n=67 (34 successful), 1 year n=50 (22 successful)
ApoB: baseline n=33 (17 successful), 1 year n=22 (14 successful)
ALT: baseline n=37 (21 successful), 1 year n=31 (20 successful)
AST: baseline n=37 (21 successful), 1 year n=31 (20 successful)
Insulin (fasting): baseline n=39 (16 successful), 1 year n=14 (3 successful)
Glucose (fasting): baseline n=69 (36 successful), 1 year n=53 (25 successful)
Abbreviations: ACR: albumin – creatinine ratio
ALT: alanine aminotrasferase
ApoB: apolipoprotein B
AST: aspartate aminotransferase
BMI: body mass index
Chol: cholesterol
DBP: diastolic blood pressure
G_f: fasting glucose
HbA_{1c}: glycosylated hemoglobin
HDL: high density lipoprotein cholesterol
I_f: fasting insulin
LDL: low density lipoprotein cholesterol
SBP: systolic blood pressure
TG: triglycerides

Table A 3. Responses to physical activity questionnaire categorized by success with lifestyle monotherapy.

Physical Activity	Percentage	
	Successful	Unsuccessful
Over the past 7 days, on how many days were you physically active for a least 60 min/day?		
0-2 days	18	18
3-4 days	24	27
5-7 days	59	55
Over a typical or usual week, on how many days are you physically active for a total of at least 60 min/day?		
0-2 days	29	0
3-4 days	12	55
5-7 days	59	45
*What types of activity do you do?**		
Endurance	82	91
Flexibility		9
Strength		36
No answer	18	11
Have you changed the amount or type of activity you do after being diagnosed with T2D/ or after being told you were at risk of developing T2D?		
Yes	65	73
No	35	27
About how many hours a day do you usually watch television (including videos) in your free time on weekdays?		
0-2 hours/day	76	55
3-4 hours/day	24	36
5->7 hours/day		9
About how many hours a day do you usually watch television (including videos) in your free time on weekends?		
0-2 hours/day	65	45
3-4 hours/day	18	9
5->7 hours/day	18	45
About how many hours a day do you usually use a computer (for playing games, emailing, chatting or surfing the Internet) in your free time on weekdays?		
0-2 hours/day	76	82
3-4 hours/day	18	18
5->7 hours/day	6	
About how many hours a day do you usually use a computer (for playing games, emailing, chatting or surfing the Internet) in your free time on weekends?		
0-2 hours/day	82	82
3-4 hours/day		
5->7 hours/day	18	18
About how many hours a day do you usually spend doing school homework out of school hours on weekdays?		
0-2 hours/day	94	64
3-4 hours/day	6	9
5->7 hours/day		9
Not applicable (youth not attending school)		15
About how many hours a day do you usually spend doing school homework out of school hours on weekends?		
0-2 hours/day	94	64
3-4 hours/day	6	9
5->7 hours/day		9
Not applicable (youth not attending school)		15
Is this different than what you did before you were diagnosed with T2D?		
Yes	53	73
No	47	27

*When sum of percentages >100%, respondents chose greater than one option (i.e. endurance and strength exercise)

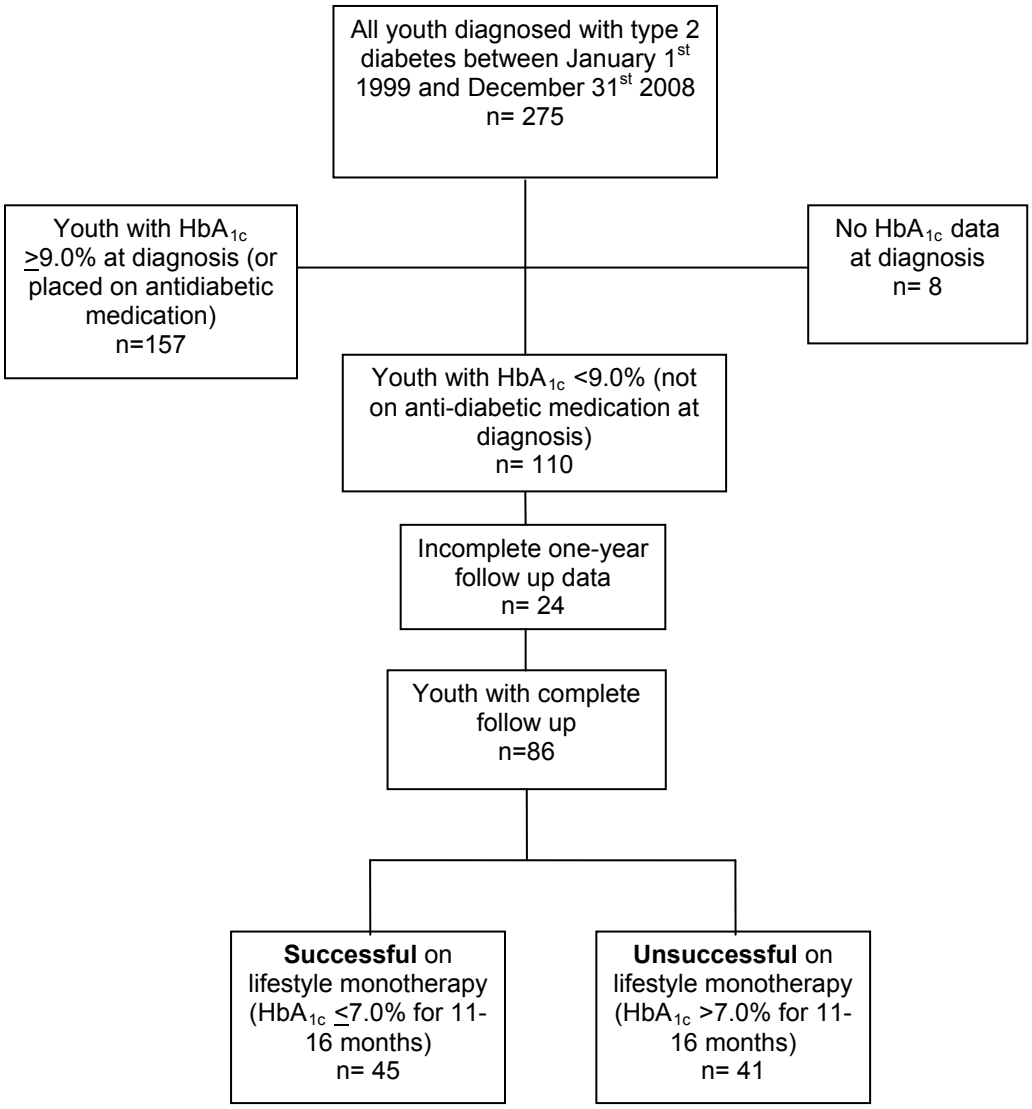
Table A 4. Responses to nutrition questionnaire categorized by success with lifestyle monotherapy.

Diet Behaviours	Percentage	
	Successful	Unsuccessful
How often do you usually have breakfast (more than a glass of milk or fruit juice):		
During the week?		
0-3 days	53	64
4-5 days	47	36
On the weekend?		
0-1	41	45
2	59	55
How many times a week do you usually eat fruit or vegetables?		
0-4 days	47	55
5->7 days	53	45
How many times a week do you usually eat sweets (candy, chocolate or other)?		
0-4 days	82	100
5->7 days	18	0
How many times a week do you usually drink Coke or other soft drinks that contain sugar?		
0-4 days	71	82
5->7 days	29	18
Have you changed the amount of sugar containing drinks including soda since you have been diagnosed with type 2 diabetes?		
yes	76	64
no	24	36
If yes, have you increased or decreased the amount of soda or sugar containing drinks you drink in a week?		
Increased		9
Decreased	76	55
No answer	24	36

Figures Study A.

Figure A 1: Selection of cohort.

Subjects were divided into subgroups by HbA_{1c} at 11-16 month follow-up as successful with lifestyle monotherapy (HbA_{1c} <7.0%) or unsuccessful with lifestyle monotherapy (HbA_{1c} ≥7.0%).



Chapter 4

Study B.

Physical Activity, Cardiorespiratory Fitness, Intrahepatic Lipid and Glucose Tolerance in Adolescents

RATIONALE

Type 2 diabetes is one of the fastest growing chronic illnesses worldwide (Zimmet, Alberti et al. 2001). This trend is not restricted to adults, as the clinical incidence of pediatric type 2 diabetes accounts for up to 80% of new cases of diabetes in various pediatric endocrinology clinics. The majority of studies of youth with type 2 diabetes focus on co-morbidity profiles at diagnosis. Therefore little information exists pertaining to modifiable lifestyle factors associated with a diagnosis of type 2 diabetes in adolescence (McGavock, Sellers et al. 2007). A better understanding of the lifestyle factors associated with the loss of glucose tolerance in youth would provide important insight into the natural history of type 2 diabetes and inform therapeutic targets for disease prevention. We hypothesized that both cardiorespiratory fitness and physical activity levels would be reduced in youth with type 2 diabetes versus overweight and non-overweight normoglycemic controls. A secondary hypothesis was that levels of intracellular lipid (steatosis) would be increased in youth with type 2 diabetes.

METHODS

To test the primary study hypothesis we performed a cross-sectional study of physical activity and cardiorespiratory fitness in adolescents 13-18 years of age with impaired glucose tolerance or physician-diagnosed type 2 diabetes (n=29), as well as overweight (n=81) and non-overweight (n=14) normoglycemic age matched control subjects. Type 2 diabetes and impaired glucose tolerance were

diagnosed using the criteria published by the Canadian Diabetes Association (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008). Exclusion criteria included treatment with corticosteroids or atypical antipsychotics; injury or chronic illness that would prevent participation in the exercise test and weight loss in the previous six months. Youth with type 2 diabetes treated with insulin (n=4) were instructed to withhold the morning dose on the day of intravenous glucose tolerance testing. Normoglycemic youth were recruited from the community using radio and newspaper advertisements, and youth with type 2 diabetes were recruited during clinical visits at the DERCA. All participants and parents provided written informed consent to participate in the study, which was approved by the Biomedical Research Ethics Board at the University of Manitoba and performed according to the Declaration of Helsinki.

Screening

At the first visit, medical and family history was taken and ethnicity was self-reported from parent or guardian. This was followed by a 2-hour 75 gram glucose tolerance test.

Outcome Measures

Primary Outcomes: Cardiorespiratory Fitness and Physical Activity Levels.

Cardiorespiratory fitness was determined directly from a graded maximal cycle ergometer test to exhaustion as previously described (McGavock, Mandic et al. 2004). Subjects were instructed to attempt to maintain a cadence ≥ 60

revolutions per minute during the test. The initial workload was set at 30 watts and increased by ~30 watts every two minutes, until subjects achieved a respiratory exchange ratio of > 1.0, (generally corresponding to an rate of perceived exertion (*RPE)* of 13) after which the workload was increased every one minute until exhaustion. Heart rate was continuously recorded, while blood pressure and RPE were assessed at two minute intervals. Oxygen consumption was measured with indirect calorimetry (Parvomedics True One®, Sandy, UT). Gas calibration (CO_2 and O_2) and flow meter calibration using a 3 L syringe were performed prior to each exercise test. During the test, expired gases were sampled every 15 seconds. Peak oxygen uptake was calculated as the average oxygen consumption rate during the last minute of the test. Absolute rates of oxygen uptake at peak exercise were normalized to body mass and fat free mass for group-wise comparisons. Youth unable to achieve a respiratory exchange ratio of at least 1.05 were excluded from the final analyses.

Daily physical activity levels were measured objectively using a waist-mounted pedometer (SC01 Stepcounts™, Deep River ON, Canada) worn over a period of 7 days in a subgroup of participants (Tudor-Locke, Lee et al. 2006). To determine the pedometer accuracy, a research assistant positioned the pedometer on the subject's right hip, slightly anterior to the mid-axillary line and instructed the subject to walk 50 steps. If the pedometer registered more than ± 3 steps from 50, the pedometer was repositioned and the process was repeated until step

counts fell within the acceptable range (Horvath, Taylor et al. 2007). Subjects were provided with a 7-day calendar to record daily pedometer steps, and self-report daily physical activities. Youth were instructed to wear the pedometer from the time they woke up until the time they went to bed (excluding water activities), and to reset the pedometer every night after recording the data.

Secondary Outcomes: Intracellular lipid content and Insulin Sensitivity.

Magnetic resonance imaging (MRI) and spectroscopy (^{1}H-MRS) were used to assess visceral fat and tissue triglyceride respectively. Magnetic resonance imaging was performed using a 1.5-T whole-body magnet (General Electric Medical Systems, Milwaukee, WI) as previously described (Szczepaniak, Babcock et al. 1999). In vivo MRS with a 10-20mm^3 single voxel volume of interest was used to collect ^{1}H spectra from the soleus and liver respectively. In brief, high resolution images were obtained in three planes using standard clinical techniques and a voxel was placed in an area devoid of subcutaneous or visceral fat or vessels for the collection of proton spectra. A total of 64 spectra were collected and averaged for the determination of intracellular lipid content in both the soleus and liver. LC Model software (Provencher 2001) was used to isolate peaks at 1.4 (intramyocellular) and 1.6 ppm (extramyocellular) and quantify the area under each peak. Visceral fat was assessed using high-resolution magnetic resonance imaging at a level between the 3rd and 5th lumbar vertebrae as previously described (Zib, Jacob et al. 2007) and quantified off-line

using Slicer3 software (Version 3.21; Boston, MA). Due to size restrictions, five overweight controls and four youth with impaired glucose tolerance / type 2 diabetes were unable to participate in magnetic resonance imaging and dual energy x-ray absortiometry measurements.

Insulin Sensitivity.

Participants underwent a modified frequently sampled intravenous glucose tolerance test with use of exogenous insulin to determine insulin sensitivity (Ball, Shaibi et al. 2004). Fasting blood samples were collected prior to an intravenous bolus of a 25% glucose solution (0.3 g/kg body weight) at time 0, followed by an intravenous bolus of regular human insulin (0.03 U/kg body weight) at 20 minutes. Blood samples for glucose and insulin were collected at 1, 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140 and 180 minutes. Glucose and insulin kinetics were then modeled using the Bergman Minimal Model with customized software (MINMOD) to quantify insulin sensitivity and beta cell function (Boston, Stefanovski et al. 2003). Negative acute insulin response values obtained from youth with type 2 diabetes were set to zero for analyses as previously described (Harris, Gittelsohn et al. 1997). Plasma glucose was measured on a Roche Modular P analyzer with a UV test principle (hexokinase method). Insulin was measured on an Immulite, solid-phase, two-site chemiluminescent immunometric assay. Serum lipoproteins and triglycerides were measured on a Roche Modular P analyzer. The coefficient of variation was

5.3-6.4% for insulin analyses and 1.2-1.4% for glucose, with a sensitivity of 14.4 pmol and 0.1 mmol/L respectively.

Confounding / exploratory outcome measures: Adiposity, waist and hip circumference.

Dual energy x-ray absortiometry (DXA; Hologic, Bedford MA, USA) was used to quantify fat mass (kg), fat free mass (kg) and percent body fat. The DXA machine was calibrated daily prior to study use with standardized phantom scanning protocols as manufacturer specifications and DXA scans were administered by a certified DXA technologist. Waist and hip circumferences were measured to the nearest 0.1 cm. Waist circumference was measured using the top of the iliac crests as a landmark and the widest point of the hips was measured to determine hip circumference. Measures were taken in duplicate with a flexible tape measure and the average of the two measures was used.

Statistical Analyses

All data are presented as means and standard deviations, unless otherwise stated. Youth were stratified into one of three categories according to their glucose tolerance and weight status; (1) Non-overweight normoglycemic youth (n=14); (2) Overweight normoglycemic youth (n=81) and (3) Overweight youth with impaired glucose tolerance or type 2 diabetes (n=7/22). Overweight status was defined by BMI values exceeding age and sex-specific cut-points established by the International Obesity Task Force (Cole, Bellizzi et al. 2000).

Youth with impaired glucose tolerance and type 2 diabetes were combined into one group (impaired glucose tolerance / type 2 diabetes) as the sample size prohibited separate analysis of youth with impaired glucose tolerance. Chi-squared tests were used to determine if differences existed in sex or ethnicity across the three groups.

Continuous variables were visually inspected for a normal distribution or skewness, as well as statistically tested with trended and detrended Q-Q plots. The following data were not normally distributed and subsequently log transformed for analyses: liver fat, BMI z-score, insulin sensitivity, triglycerides, VO_{2peak} (L/min), VO_{2peak} (ml/kg/min), body fat, HOMA and visceral fat. Data are presented in their untransformed format. Analysis of variance with Tukey's post hoc analysis was used to test for group-wise differences in the secondary outcomes. Continuous associations between peak oxygen uptake and metabolic risk factors for type 2 diabetes were determined using bivariate and partial correlation analyses. Multiple linear regression was used to test for associations between intrahepatic lipid content and insulin sensitivity after controlling for sex and ethnicity. All analyses were performed with PASW version 18.0 (SPSS/IBM, Chicago). A $p < 0.05$ was considered statistically significant.

RESULTS

Subject Characteristics

Of the 137 youth screened, seven (two with type 2 diabetes and five overweight

normoglycemic youth) were excluded for not achieving respiratory exchange ratio values of >1.05. Six were excluded for unreliable MINMOD data due to severely hemolyzed blood samples. Seven overweight youth were diagnosed with impaired glucose tolerance during screening and grouped with the 22 youth diagnosed with type 2 diabetes. One hundred twenty four youth remained in the final analysis (Table B 1).

The impaired glucose tolerance / type 2 diabetes group comprised a greater proportion of First Nations youth compared to the overweight normoglycemic group (76% vs. 24%, $p<0.01$). As a result, a sub-analysis was performed within the overweight normoglycemic group to determine whether characteristics differed by ethnicity (Table B 2). There were no significant differences in the variables tested between overweight normoglycemic First Nation and non-First Nation youth therefore the remaining analyses were conducted with overweight normoglycemic youth of all ethnicities combined.

As expected, percent body fat and BMI z-score were higher in youth who were overweight or had impaired glucose tolerance / type 2 diabetes, relative to the non-overweight controls ($p<0.001$). There was no difference in body fat or BMI z-score between youth with impaired glucose tolerance / type 2 diabetes and the overweight normoglycemic group (Table B 1). Waist circumference was higher in youth with impaired glucose tolerance / type 2 diabetes compared with overweight normoglycemic youth, however visceral fat mass measured by

magnetic resonance imaging was not.

Primary Outcome Measures

As hypothesized, peak oxygen uptake expressed relative to body mass and lean body mass was significantly reduced in youth with impaired glucose tolerance / type 2 diabetes relative to both their overweight and non-overweight normoglycemic peers (Figure B 1, Table B 3). Similarly, peak workload indexed to lean body mass was also lowest in youth with impaired glucose tolerance / type 2 diabetes. Youth with impaired glucose tolerance / type 2 diabetes were also characterized by a lower heart rate and respiratory exchange ratio at peak exercise compared to both overweight and non-overweight normoglycemic controls. Rate of perceived exertion did not differ between groups. Physical activity was below recommended levels in all groups (Table B 1), however weekly step counts were lower in youth with impaired glucose tolerance / type 2 diabetes compared to non-overweight normoglycemic youth ($p=0.004$).

Secondary outcome Measures: Cardiometabolic risk factors

Youth with impaired glucose tolerance / type 2 diabetes were characterized by levels of intrahepatic lipid over two-fold higher than overweight normoglycemic controls (Figure B 2; $p = 0.001$) with no difference in intramuscular triglyceride content between groups (Table B 4). Further, youth with impaired glucose tolerance / type 2 diabetes were characterized by significantly reduced insulin sensitivity ($p=0.001$), higher levels of estimated insulin resistance (HOMA,

p=0.001) and elevated triglycerides (p=0.003) compared to both normoglycemic control groups (Table B 4). Systolic blood pressure was also higher in youth with impaired glucose tolerance / type 2 diabetes (p=0.02), although this became non significant with post-hoc testing (p=0.06 versus both non-overweight and overweight controls).

Associations: In bivariate analyses, cardiorespiratory fitness expressed relative to total body mass or fat free mass was negatively associated with intahepatic lipid (Figure B 3; VO_{2peak} ml/kgFFM/min; r= -0.4, p<0.001). There was an inverse relationship between cardiorespiratory fitness and waist circumference as well as serum triglycerides; and a positive association between cardiorespiratory fitness and insulin sensitivity (Table B 5). The relationship between cardiorespiratory fitness and hepatic triglyceride persisted when the three youth with extreme levels of hepatic triglyceride (>30%) were removed from the analysis (r= -0.4 p=0.001), and when body fat and BMI z-score were controlled for using a partial correlation analysis. Intrahepatic lipid content was inversely associated with insulin sensitivity (r= -0.40, p<0.001).

Using a hierarchical multiple linear regression model, intrahepatic lipid content and waist circumference were found to be the best predictors of insulin sensitivity (Table B 6). These relationships were independent of ethnicity and sex.

DISCUSSION

This comprehensive study of adolescents spanning the natural history of type 2

diabetes revealed that cardiorespiratory fitness is lower in youth with impaired glucose tolerance / type 2 diabetes and associated with several risk factors for type 2 diabetes. Additionally, we observed that physical activity levels are substantially lower among youth with type 2 diabetes and far below current recommended guidelines for optimal growth and health in youth (Tudor-Locke, Pangrazi et al. 2004). Daily pedometer steps were also lower across all three groups in the present study compared to recently reported national data from the CANPLAY study (Canadian Physical Activity Levels Among Youth) (Craig, Cameron et al. 2010). This difference was most dramatic in youth with impaired glucose tolerance or type 2 diabetes who took approximately 50% less steps per day than the average Canadian youth as represented by CANPLAY data.

Third, intrahepatic lipid content is markedly elevated in youth with impaired glucose tolerance / type 2 diabetes and inversely associated with both insulin sensitivity and fitness in youth. Collectively, these data suggest that measures of physical activity, cardiorespiratory fitness and intrahepatic lipid content may serve as predictive biomarkers of impaired glucose tolerance / type 2 diabetes in overweight youth.

Previous studies demonstrate that low cardiorespiratory fitness increases the risk of obesity and the clustering of metabolic abnormalities in youth, conditions preceding type 2 diabetes (Froberg and Andersen 2005; Janssen and Cramp 2007). The current data extend these findings, and support prior observations in

smaller cohorts of youth by demonstrating that low cardiorespiratory fitness is a characteristic feature of youth with impaired glucose tolerance and type 2 diabetes (Faulkner, Quinn et al. 2005; Gusso, Hofman et al. 2008; Shaibi, Faulkner et al. 2008; Nadeau, Zeitler et al. 2009). Fitness may be an important clinical measure in our attempts to monitor and predict the development of type 2 diabetes in overweight adolescents.

The accumulation of intrahepatic lipid (steatosis) is common in adults with type 2 diabetes (Kotronen, Juurinen et al. 2008); and associated with abdominal obesity, metabolic abnormalities and insulin resistance in youth (Taksali, Caprio et al. 2008). While other investigators have documented that metabolic risk factor clustering occurs more frequently and to a greater degree in youth with elevated intrahepatic lipid (Weiss, Dufour et al. 2003; Taksali, Caprio et al. 2008), none have included youth with type 2 diabetes. The over 2-fold difference in intrahepatic lipid content between the youth with impaired glucose tolerance / type 2 diabetes and overweight normoglycemic peers strongly supports the theory that dysregulated lipid metabolism plays a key role in the progression to dysglycemia (Kotronen and Yki-Jarvinen 2008). In agreement with others (Burgert, Dziura et al. 2006), these differences are evident in the absence of clinically elevated levels of serum transaminases, implying that intrahepatic lipid accumulates early in the pathogenesis of type 2 diabetes and may be an important biomarker of type 2 diabetes in youth. Similar to previous studies of

overweight youth (Weiss, Dufour et al. 2003), a negative association was observed between spectroscopy-derived intrahepatic lipid content and insulin sensitivity, supporting the growing body of evidence that steatosis is a biomarker of type 2 diabetes and may also play a causal role in the natural history of the disease.

The mechanism underlying the elevated intrahepatic lipid content observed in individuals with impaired glucose tolerance / type 2 diabetes is likely the result of an uncoupling between the mobilization of free-fatty acids from adipocytes and oxidation of lipids within hepatocytes (Taksali, Caprio et al. 2008). Recent cross sectional (Krasnoff, Painter et al. 2008) and intervention studies (Larson-Meyer, Heilbronn et al. 2006) in adults suggest that increased physical activity may prevent this uncoupling and attenuate lipid accumulation in the liver. The current findings extend these observations to youth by demonstrating a negative association between cardiorespiratory fitness and intrahepatic lipid content, independent of measures of adiposity. A recent intervention trial in a small number of Hispanic youth demonstrated that 12 weeks of vigorous exercise can reduce hepatic steatosis and improve measures of insulin sensitivity in obese youth (van der Heijden, Wang et al. 2010). Larger randomized controlled intervention studies in youth are needed to confirm these findings and determine the dose of exercise required to reduce intrahepatic lipid content, especially among overweight youth at risk for type 2 diabetes.

Limitations

As with previous reports of type 2 diabetes in Canadian cohorts (Hanley, Harris et al. 2005; Sellers, Blydt-Hansen et al. 2009), the current sample is disproportionately represented by First Nations youth. Differences in ethnicity had limited impact on our findings as fitness was not different across ethnic groups and ethnicity was not a significant covariate in multiple linear regression models predicting insulin sensitivity. Further, there were no baseline differences between overweight normoglycemic First Nation and non-First Nation youth (Table B 2). The average maximal heart rate was lower in youth with impaired glucose tolerance / type 2 diabetes relative to normoglycemic overweight controls, however this is similar to previous studies of adults (Fang, Sharman et al. 2005) and youth with type 2 diabetes (Gusso, Hofman et al. 2008; Shaibi, Faulkner et al. 2008) and may be indicative of early autonomic dysfunction (Poirier, Bogaty et al. 2003). The observation that average step counts and peak work capacity were significantly lower in youth with impaired glucose tolerance / type 2 diabetes suggests that physical activity patterns contributed to reduced fitness levels. Finally, the cross sectional design precludes determination of the causal nature of the associations described. Accordingly, longitudinal or intervention studies are needed to confirm the observation that low physical activity and fitness and elevated intrahepatic lipid content are risk factors for impaired glucose tolerance / type 2 diabetes in youth.

In conclusion, low fitness is a characteristic feature of and is associated with risk factors for type 2 diabetes in youth, in particular intrahepatic lipid content. These data provide new insight into novel biomarkers and potential modifiable risk factors for the prevention of type 2 diabetes in youth.

Tables Study B.

Table B 1. Participant Characteristics

Variable	*Non-overweight*	*Overweight*	*Impaired Glucose Tolerance / Type 2 Diabetes*
n	14	81	29
Age (years)	16.3 (1.9)	15.1 (2.3)	15.5 (1.5)
Sex (male/female)	5/9	26/55	12/17
Ethnicity (CS/FN/Other)	12/1/1	51/21/9	4/22/3*†
Body mass (kg)	60.6 (10.7)	87.8* (18.2)	99.0*† (22.2)
BMI z-score	0.2 (0.6)	1.9* (0.5)	2.1* (0.5)
Body fat (%)	23.7 (6.4)	37.2* (5.6)	37.7* (6.8)
Fat free mass (kg)	44.2 (7.6)	52.0* (9.5)	60.0*† (11.6)
Waist circumference (cm)	74.2 (7.7)	100.9* (16.5)	111.4*† (16.0)
Hip circumference (cm)	92.4 (6.4)	109.0* (13.7)	110.5* (11.0)
Visceral fat (cm^2)	64.1 (14.5)	90.5 (49.0)	103.7* (35.0)
Subcutaneous fat (cm^2)	124.6 (66.3)	336.3* (148.8)	320.4* (121.2)
Average weekly steps (steps/day)	8908 (2949)	6837 (2521)	4905* (2075)
Average weekday steps (steps/day)	9161 (3015)	7416 (3051)	5021* (2204)
Average weekend steps (steps/day)	7885 (3110)	5550 (2698)	5161 (3169)

*$p<0.05$ vs. Non-overweight youth
†$p<0.05$ vs. Overweight youth

Table B 2. Baseline characteristics of overweight normoglycemic participants comparing First Nation and non-First Nation youth.

Variable	*Overweight non-First Nation (normoglycemic)*	*Overweight First Nation (normoglycemic)*
n	60	21
Age (years)	15.3 (1.8)	14.8 (3.3)
Sex (male / female)	20/40	6/15
Body mass (kg)	87.1 (17.3)	90.1 (21.2)
BMI z-score	1.9 (0.4)	1.9 (0.5)
Body fat (%)	37.9 (5.6)	35.1 (5.2)
Fat free mass (kg)	51.4 (9.0)	53.9 (10.9)
Waist circumference (cm)	99.2 (16.9)	105.9 (14.2)
Hip circumference (cm)	108.8 (14.8)	109.6 (10.0)
Visceral fat (cm^2)	91.0 (35.9)	111.1 (92.6)
Subcutaneous fat (cm^2)	288.2 (96.1)	263.9 (50.6)
Intrahepatic lipid content (%fat/water)	5.6 (6.0)	5.8 (7.1)
Average weekly steps (steps/day)	7321 (2425)	5097 (2148)
Average weekday steps (steps/day)	7522 (2800)	7079 (3880)
Average weekend steps (steps/day)	6034 (2715)	4007 (2062)

Table B 3. Fitness characteristics of groups.

Variable	*Non-overweight*	*Overweight*	*Impaired glucose tolerance / Type 2 diabetes*
VO_{2peak} (ml/kgFFM/min)	50.1 (8.1)	43.7 (6.2)*	39.3 (6.9)*†
VO_{2peak} (ml/kg/min)	36.0 (6.6)	26.7 (6.0)*	23.4 (5.9) *†
VO_{2peak} (L/min)	2.2 (0.7)	2.3 (0.5)	2.3 (0.5)
Workload (watts/kgFFM)	4.2 (0.9)	3.3 (0.6)*	2.8 (0.6)*†
Workload (watts)	188.7 (59.0)	172.5 (43.1)	164.3 (41.6)
HRmax	188.5 (12.6)	187.8 (10.5)	179.3 (11.7) *†
RER	1.21 (0.1)	1.19 (0.1)	1.14 (0.1)*†
RPE	17.4 (2.2)	16.4 (3.5)	17.2 (2.0)

*p<0.05 vs. Non-overweight youth
†p<0.05 vs. Overweight youth

VO_{2peak}: peak oxygen consumption
HRmax: maximal heart rate achieved on exercise test
RER: respiratory exchange ratio
RPE: rate of perceived exertion

Table B 4. Cardiometabolic Characteristics

Variable	*Non-overweight*	*Overweight*	*Impaired Glucose Tolerance / Type 2 Diabetes*
HbA_{1c} (%)	--	--	7.2 ± 1.6
Intraheptaic TG (%Fat/Water)	1.4 (1.4)	5.6 (6.2)*	13.0 (14.1)* †
Intramuscular TG (% Fat/Water)	0.5 (0.4)	1.4 (2.4)	1.8 (2.2)
AST (U/L)	22.7 (5.6)	24.2 (11.7)	26.1 (11.9)
ALT (U/L)	15.1 (4.0)	24.3 (20.2)	32.2 (27.0)*
Insulin sensitivity ($mU\ kg^{-1}\ min^{-1}$)	9.1 (4.3)	3.9 (2.6)*	2.7 (3.3)* †
Acute insulin response (mU/l)	241.4 (130.4)	691.8 (469.0)*	295.4 (534.3) †
HOMA	1.3 (0.7)	3.9 (5.1)*	9.4 (10.2) *†
Triglycerides (mmol/L)	0.9 (0.6)	1.2 (0.8)	2.0 (1.4)* †
HDL (mmol/L)	1.5 (0.3)	1.2 (0.3)*	1.1 (0.3)*
LDL (mmol/L)	2.3 (0.6)	2.4 (0.7)	2.4 (0.7)
SBP (mmHg)	109.6 (16.2)	114.4 (12.9)	127.5 (16.0)* †
DBP (mmHg)	62.9 (6.4)	64.1 (8.5)	69.3 (10.4) †

*= $p < 0.05$ vs. Non-overweight
† = $p < 0.05$ vs. Overweight

HOMA: homeostatic model assessment
AST: aspartate aminotransferase
ALT: alanine aminotransferase
SBP: systolic blood pressure
DBP: diastolic blood pressure

Table B 5. The association between cardiorespiratory fitness and select cardiometabolic risk factors

Variable	*Peak Fitness (ml/kg/min)*		*Peak Fitness (ml/kgFFM/min)*	
	Pearson r	Significance	Pearson r	Significance
Intrahepatic lipid	-0.39	p<0.001	-0.36	p<0.001
Insulin sensitivity	0.33	p=0.001	0.24	p=0.016
Triglycerides	-0.33	p<0.001	-0.34	p<0.001
Waist circumference	-0.70	p<0.001	-0.48	p<0.001

Association assessed using Pearson's correlation coefficient.

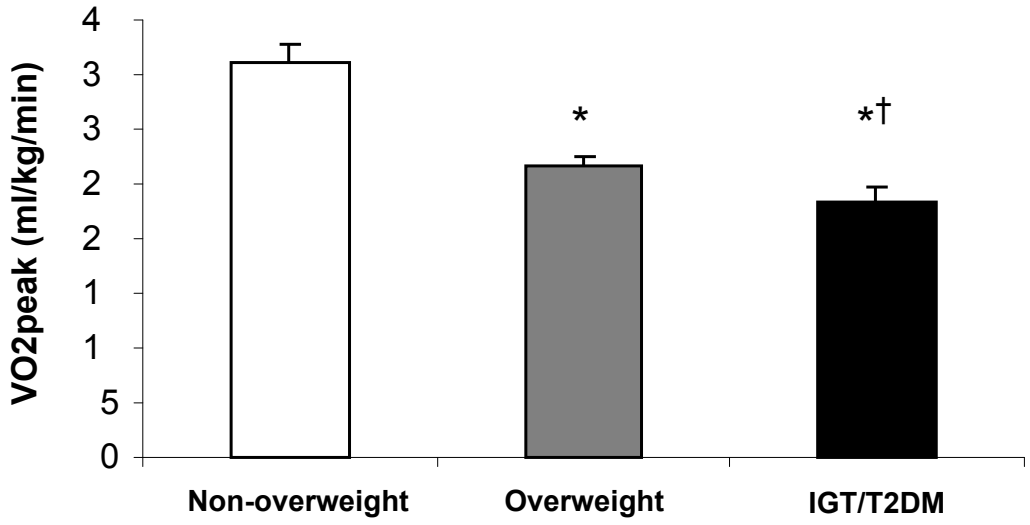
Table B 6. Intrahepatic lipid content and waist circumference are associated with insulin sensitivity independent of sex and ethnicity.

Model	*Variable*	*Standardized ß*	*P-value*	R^2 *change*
1	Sex	0.10	0.33	0.05
	Ethnicity	-0.18	0.08	
2	Sex	0.04	0.73	0.25
	Ethnicity	-0.06	0.55	
	Fitness (ml/kgFFM/min)	-0.01	0.93	
	Intrahepatic lipid (%Fat/Water)	-0.23	0.03	
	Body fat (%)	-0.12	0.38	
	Waist circumference (cm)	-0.46	0.03	

Dependant variable: Insulin sensitivity

Model: r=0.55, p<0.005
*p-value in table denotes individual contribution to overall model

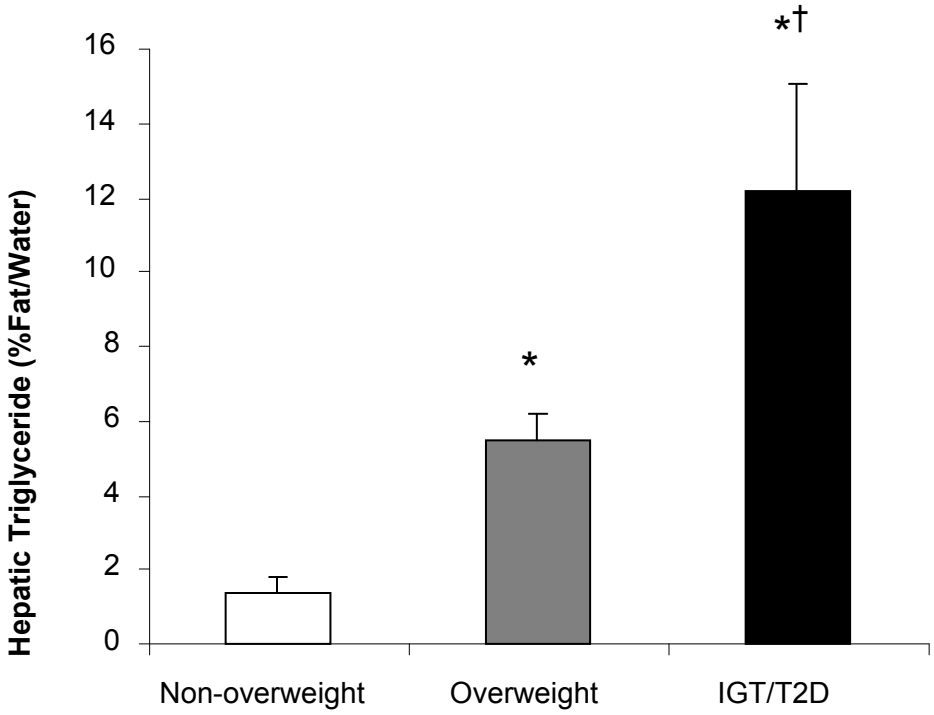
Figure B 1. Cardiorespiratory fitness is reduced in youth with impaired glucose tolerance / type 2 diabetes.



* p<0.05 versus non-overweight youth
† p<0.05 versus overweight youth

Data presented as mean (standard error).
IGT/T2DM: Youth with impaired glucose tolerance / type 2 diabetes

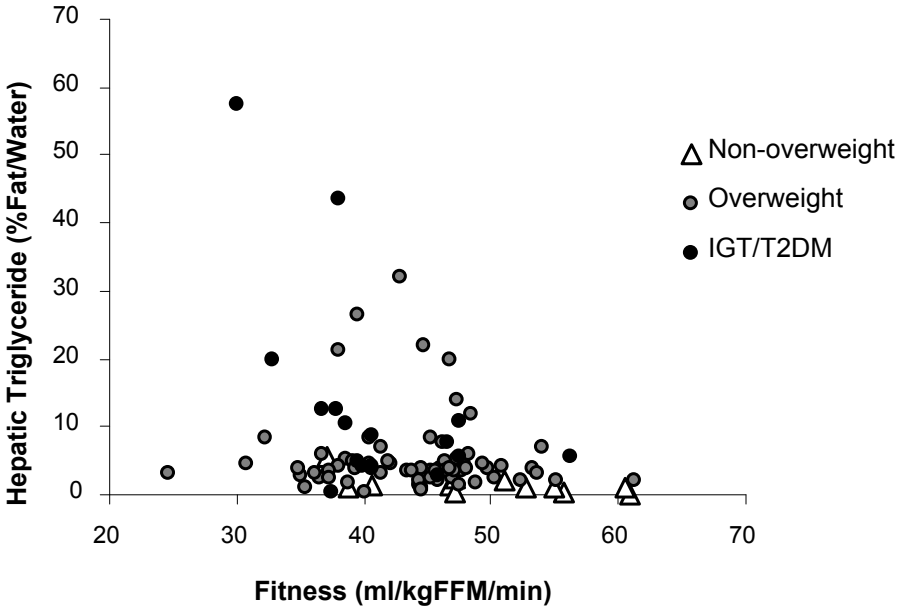
Figure B 2. Intrahepatic lipid content is increased in youth with impaired glucose tolerance / type 2 diabetes compared with non-overweight and overweight controls.



* p<0.05 versus non-overweight youth
† p<0.05 versus overweight youth

Data presented as mean (standard error).
IGT/T2DM: Youth with impaired glucose tolerance / type 2 diabetes

Figure B 3. Intrahepatic lipid content is associated with fitness.



R=0.4, p<0.001

IGT/T2DM: Youth with impaired glucose tolerance / type 2 diabetes

Chapter 5

Study C.

The POWER Trial: Interim analysis

RATIONALE

In Canada, 30% of adolescents are considered overweight and a number of these are at significant risk for type 2 diabetes. Studies in adults demonstrate that physical activity reduces the risk for type 2 diabetes in a dose-response manner (Kang, Kelley et al. 1999; Kraus, Torgan et al. 2001). A similar body of evidence does not exist in overweight youth.

Cross sectional and small experimental trials suggest that higher intensity activity (i.e. moderate to vigorous intensity) is associated with superior improvements in insulin sensitivity in youth when compared with lower intensity activity (Kang, Gutin et al. 2002; Rizzo, Ruiz et al. 2008). The purpose of this study was to conduct an adequately powered, randomized controlled trial of physical activity differing in intensity to confirm these observations.

Accordingly the primary aim of this study is to compare the effects of aerobic exercise training regimens differing in intensity (relative to peak cardiorespiratory fitness) on insulin sensitivity in overweight youth. The secondary aim is to assess the effect of physical activity on tissue lipid content in overweight youth. Our hypothesis is that improvements in insulin sensitivity and tissue lipid content will be greater following high intensity physical activity in comparison to low intensity physical activity in overweight adolescents 13-18 years old and at risk for type 2 diabetes.

METHODS

The POWER Trial is a randomized controlled clinical trial (clinical trial registration identifier: NCT00755547). We will ultimately randomly assign 120 overweight adolescents with risk for type 2 diabetes to: (i) a low intensity continuous physical activity arm (40-55% of heart rate reserve), (ii) a high intensity intermittent physical activity arm (70-85% of heart rate reserve) or (iii) a control group. The intervention arms differ by training intensity, however the duration of training sessions are adjusted to ensure equal caloric expenditure between the two groups. The primary outcome measure of this trial is insulin sensitivity, measured directly from Bergman's frequently sampled intravenous glucose tolerance test. For the purposes of this interim analysis, data from the first 48 youth to complete the trial were examined.

Subjects. Inclusion / Exclusion Criteria

Adolescents 13 to 18 years old with a BMI considered overweight according to age and sex specific standards developed by the International Obesity Task Force (Cole, Bellizzi et al. 2000) were eligible for the POWER Trial. To increase the likelihood of enrolling an adequate number of youth with impaired insulin sensitivity, recruitment was restricted to overweight adolescents with one additional risk factor for youth-onset type 2 diabetes including: ethnic minority (Young, Reading et al. 2000); in utero exposure to hyperglycemia (i.e. mother with gestational or frank diabetes during pregnancy) (Young, Martens et al. 2002)

and / or evidence of hepatic steatosis (serum ALT > 60U/L, ultrasound or ^{1}H-MRS-based evidence of steatosis). Individuals were excluded if they had conditions that would affect the primary and secondary outcome variables and confound study results. Therefore, youth were excluded if they (1) were diagnosed with impaired glucose tolerance or type 2 diabetes; (2) were currently being treated with corticosteroids or atypical antipsychotics, as these agents significantly influence carbohydrate metabolism and insulin sensitivity (Houseknecht, Robertson et al. 2007); (3) had an orthopaedic injury or chronic illness that would prevent them from participating in the intervention; (4) had experienced weight loss or enrolled in weight loss program in the six months prior to the study; or (5) had a history of alcoholism or drug abuse.

All participants and parents provided written informed consent to participate in the study, which was approved by the Biomedical Research Ethics Board at the University of Manitoba and performed according to the Declaration of Helsinki.

Recruitment and Screening

Overweight normoglycemic youth from study B were offered participation in the POWER Trial provided they met all inclusion criteria, as outlined in Figure C 1. To reach the target sample size, additional youth aged 13 to 18 years continued to be recruited from the community via advertisements. POWER Trial advertisement included posters hung in doctors offices and community facilities, dissemination to health care professionals including physiotherapists and

dietitians, as well as newspaper (Winnipeg Free Press, local community papers) and radio advertising (HOT 103.1FM, QX 104.1FM).

Youth meeting inclusion criteria were screened for glucose tolerance with a 2 hour 75 gram oral glucose tolerance test, using the criteria established by the Canadian Diabetes Association (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008). Ethnicity was self-reported from a parent or guardian.

Outcome Measures

The primary outcome for this trial was insulin sensitivity measured directly with a frequently sampled intravenous glucose tolerance test (FSIVGTT). The secondary outcome was intrahepatic lipid content quantified with proton magnetic resonance spectroscopy (^{1}H-MRS). Subjects were instructed to refrain from exercising for 48 hours prior to the FSIVGTT and MRI at baseline and follow-up. Follow-up assessments were scheduled within one week of completion of the 6 month exercise trial. Confounding / exploratory variables included cardiorespiratory fitness (VO_{2peak} from a cycle ergometer test to exhaustion), physical activity (7 days of pedometry), body fat and fat free body mass (dual energy x-ray absortiometry). For calculation of heart rate reserve (HRR), resting pulse was measured in triplicate with an automated sphygmomanometer in conjunction with resting BP measures. Prior to measurement, the subject was seated in a quiet room for a minimum of five minutes. For a more detailed

description of outcome measures please refer to Study B; Methods.

Randomization

After completing baseline testing, all eligible subjects were entered into a 2 week run-in phase. Prior to randomization into the trial, each subject was required to attend four of six (67%) supervised training sessions at the YMCA-YWCA (YMCA) during the run-in phase. Youth and their parents were asked to sign a contract outlining the responsibilities of study participants once randomized, including the expected adherence rates and follow up visits (Supplement C 1). If four sessions were successfully completed within the allotted time, subjects were provided with an opaque envelope containing a letter corresponding to their group allocation (low intensity, high intensity or control group). Those who did not successfully complete the run-in phase were not randomized into the trial. Randomization was achieved using an on-line random number generator.

Youth randomized to one of the exercise arms were provided with a training log book and a Polar© heart rate monitor to use for the duration of the trial, while those randomized to the control arm were instructed to continue with their regular level of physical activity for the next 6 months. Randomization was blocked by groups of 15 (five low intensity, five high intensity and five control).

Intervention

Location.

Training occurred at each of the four YMCA's in Winnipeg Manitoba. Youth were

free to choose their preferred training location and could train at more than one location over the course of the trial.

Frequency.

Youth were expected to train 3 times per week. A team of trainers (study personnel) provided coverage to allow supervised exercise sessions 3 days per week at each of the YMCA's. Youth were allowed to perform exercise sessions without supervision provided they wore their heart rate monitor, however in most cases they were encouraged to limit unsupervised sessions to once per week. Weekly attendance adherence was calculated as percent of weekly sessions attended such that an individual who attended 3 times per week through the entire trial would have 100% attendance, while one who attended 2 days per week would have an attendance of 67%. Weekly attendance over the 6 months of the trial was averaged to calculate each individual's overall attendance adherence.

Intensity.

Training intensity was specific to each exercise arm and individualized based on each participants HR achieved at VO_{2peak} on the cycle ergometer test to exhaustion. Heart rate targets for the low intensity arm corresponded to 40-55% heart rate reserve (HRR), while the target for the high intensity group was a heart rate corresponding to 70-85% of HRR (Kraus, Torgan et al. 2001; Kang, Gutin et al. 2002; Slentz, Duscha et al. 2004). Heart rate was monitored during each

exercise session and the average heart rate at the end of the session was recorded to determine adherence to target heart rate. Training plans were individually tailored to elicit the prescribed intensity and adjusted as fitness levels and capabilities changed throughout the trial. The low intensity group was generally prescribed continuous activities, while the high intensity group primarily performed interval work.

Duration and Dose.

Training sessions were designed to elicit equal energy expenditure between the intervention groups. Those assigned to high intensity exercised for approximately 45 minutes while the low intensity group were assigned to 60+ minutes of exercise. To estimate the individual caloric expenditure per exercise session, each subject randomized to an exercise group completed an energy expenditure test within the first month of their training. This was performed on a treadmill and evaluated using indirect calorimetry. Briefly, each subject was systematically taken through a range of workloads on a treadmill which were selected based on resting HR, maximum HR and group allocation. At each stage, once steady state exercise was achieved the youth was instructed to continue exercising for a total of 3 minutes after which a brief active rest was allowed. This was repeated at a progressively higher speed / incline three more times or as tolerated. Subsequently, the calorimetry data was analyzed such that average caloric expenditure (kcal per minute) could be estimated based on average heart rate

achieved for each exercise session (Ferguson, Gutin et al. 1999; Kang, Gutin et al. 2002).

Mode.

Various aerobic activities were used throughout the trial; however the primary mode of exercise for the low intensity group was walking while youth in the high intensity group primarily ran. Youth were free to choose other aerobic activities and also trained on stationary bikes, elliptical and stair climbing machines as well as participating in aerobic classes offered at the YMCA. Outdoor training sessions were offered as weather permitted and these included walking, running and various aerobic games (soccer, ultimate etc.). Exercise sessions began with a 5-10 minute warm up and ended with 5-10 minutes of stretching and core work (planks, sit ups, bridging at the discretion of the trainer).

Statistical analyses

All data are presented as mean (standard deviation) unless otherwise indicated. Data was tested for normalcy using Q-Q plots and visual analysis and transformed as indicated. Variables requiring log transformation included insulin sensitivity, acute insulin response, disposition index, AST, triglycerides and intrahepatic lipid. All data are displayed in their untransformed format. Baseline characteristics were summarized using descriptive statistics. Between group differences in continuous baseline characteristics were examined using an ANOVA with Tukey's test for post-hoc comparisons. Differences in categorical

variables such as sex and ethnicity were examined with Fischer's exact test. Within group change over time was analysed using paired t-tests, while the effect of group on change over time was assessed using repeated measures ANOVA. Those lost to follow up were analyzed using the intention to treat principle; therefore baseline data was imputed for missing values in these cases. Significance was defined as a $p < 0.05$ with the exception of paired t-testing where significance was adjusted to $p < 0.017$ to account for multiple comparisons.

RESULTS

Fifty three youth were randomized to the POWER trial between June 2007 and September 2009. The last follow up visit for subjects included in the current analysis occurred in March of 2010. Data from five youth were excluded due to severe hemolysis of multiple blood samples taken during the FSIVGTT; resulting in false low insulin values and rendering the FSIVGTT data unreliable (two were randomized to high intensity and three to low intensity). Subject demographics for the forty eight youth remaining in the analysis are in Table C 1. This includes data from three subjects who were randomized but did not return for follow up testing (two randomized to control, one to low intensity). As per the randomization scheme, there were no significant differences in mean baseline characteristics between groups (Table C 2).

Insulin Sensitivity

Repeated measures ANOVA indicated a significant improvement in insulin sensitivity over time (Table C 3, p=0.05) with no difference between groups (p=0.13). However only the high intensity and control group had a mean increase in insulin sensitivity from baseline to follow-up, and contrary to our primary hypothesis only the change in the control group reached significance in these preliminary analyses (paired t-test, p=0.01). Fasting insulin decreased across all groups over time (p=0.04) and accordingly insulin resistance estimated by HOMA also was reduced, although non-significant (p=0.07) with no difference between groups.

Intrahepatic lipid content

Consistent with our hypothesis, both intervention groups had a mean decrease in intrahepatic lipid content values from baseline to follow-up (non-significant), compared with an 11% increase in the control group (Figure 2).

Fitness

Group-wise baseline and follow-up fitness data are provided in Table C 4. To account for the limited sample size and variability in this preliminary data, statistical analyses of fitness data were performed with the two intervention groups collapsed into one.

There was a significant increase in absolute fitness (VO_{2peak} L/min) at follow-up in when intervention groups were collapsed into one (p=0.001) which was not

observed in the control group. Collectively, those receiving the intervention demonstrated increases in fitness indexed to body mass (pre-intervention 25.8±4.2 vs. 26.1±6.9 ml/kg/min post-intervention) and fat-free mass (43.6±4.8 vs. 44.8±6.5 ml/kgFFM/min; Figure C 3) although these relationships did not reach significance. Conversely, the control group experienced a slight decrease in fitness expressed relative to both body mass and fat free mass. Improvements in fitness tended to be associated with reductions in intrahepatic lipid (Figure C 4).

Body composition

Across all three groups, lean body mass increased significantly over time (Table C 2, $p<0.001$) with no difference between groups. Repeated measures ANOVA suggested a trend of decreasing BMI z-score over time across all groups ($p=0.06$). Waist circumference decreased in the high intensity group only and increased in the low intensity and control groups, however these changes were not significantly different likely due to large variability in the response to training.

Cardiometabolic risk factors

Follow-up evaluation by paired t-testing revealed a significant reduction in LDL cholesterol ($p=0.008$), total cholesterol ($p=0.012$) and an increase in DBP ($p=0.013$) in the low intensity group, and reduced LDL ($p=0.03$), HDL ($p=0.004$) and total cholesterol ($p=0.01$) in the high intensity group. A reduction in total cholesterol approached significance in the control group ($p=0.052$), however this

was driven primarily by a lower HDL cholesterol at follow-up.

Adherence

Ninety-six percent of youth returned for follow-up testing at 6 months (n=45). Overall trial adherence was monitored for attendance as well as exercise intensity. Attendance was similar in both groups, with those in the low intensity group attending 45.7% of the required exercise sessions, and those in the high intensity group attending 50.4%. This equates to approximately 1.5 exercise sessions per week when averaged across the groups. Sixty percent of youth in the high intensity group had an attendance adherence of > 50% compared with only 30% in the low intensity group.

On average, the low intensity group achieved a training intensity of 54.5±7.8% of HRR, while the high intensity group trained at an average of 65.4±8.1% of HRR. This corresponded with an average training HR of 137.3±8.8 bpm and 148.7±10.8 bpm respectively. Although the high intensity group on average did not meet the prescribed training intensity, both %HRR and average training HR were significantly different between groups ($p<0.005$). Weekly caloric expenditure was similar between the two groups at 326.3±88.6 kcal/session for the low intensity group and 344.1±60.8 kcal/session for those randomized to high intensity ($p=0.51$). During the period of data collection for this interim analysis, numerous strategic meetings were held to develop methods to improve adherence. These measures have been progressively implemented over the time

of data collection and are listed in Supplement C 2.

DISCUSSION

This interim analysis of the POWER Trial demonstrates that a 6 month exercise program in partnership with the YMCA may be a useful intervention to target improvements in insulin sensitivity and intrahepatic lipid content in overweight previously inactive adolescents. Although improvements in insulin sensitivity were not observed in the intervention group with these preliminary analyses, several other markers of cardiometabolic risk including intrahepatic lipid content, total cholesterol, LDL, fasting insulin, waist circumference and systolic blood pressure demonstrated trends for improvement in the intervention groups to a greater degree than the control group.

The POWER Trial began in 2007 and since that time, only one other group has evaluated the effect of exercise on both insulin sensitivity and intrahepatic lipid in youth. van der Heijden and colleagues recruited 15 post-pubertal obese Hispanic youth with high levels of intrahepatic lipid (mean ~9%) to participate in a tightly controlled 12-week intervention. Exercise sessions were supervised in a physiotherapy clinic twice per week, and performed at home the other two days per week at a prescribed intensity of ≥70%VO_{2peak}. With an adherence rate of 91%, obese youth achieved a significant improvement in insulin sensitivity and reduction in intrahepatic lipid content at follow-up. These results are promising however what remains to be established is (i) the intensity of exercise required

for improvements in insulin sensitivity and intrahepatic lipid content and (ii) whether a longer term community based intervention can elicit similar adaptations. We anticipate addressing these issues upon completion of the POWER Trial.

It is widely accepted that a single bout of exercise can improve insulin sensitivity (Bordenave, Brandou et al. 2008; Hawley and Lessard 2008; Frosig and Richter 2009) but the metabolic effects of longer term interventions are less clear, especially among youth. At 6 months duration, the POWER Trial is longer than most physical activity interventions targeting insulin sensitivity in youth, which are generally three months duration or less (Introduction; Table 1). In fact we were only able to identify four exercise trials of ≥ 6 months duration (Kang, Gutin et al. 2002; Chang, Liu et al. 2008; Kelishadi, Hashemipour et al. 2008; Tsang, Kohn et al. 2009). Only one of these longer term trials was able to demonstrate a significant improvement in insulin sensitivity with exercise training (Chang, Liu et al. 2008). There may be multiple reasons for this discrepancy, including an insufficient exercise dose or use of indirect measures of insulin sensitivity (fasting insulin, fasting glucose and HOMA). We have designed our study to overcome these limitations by using direct measures of insulin sensitivity and especially of late, closely monitoring adherence to exercise dose such that at the end of the POWER Trial it is expected that both groups will have achieved the mean prescribed exercise intensity.

Another plausible reason for non-significance in previous longer term interventions is poor overall adherence (i.e. attendance) to the prescribed program which may be exaggerated in longer-term studies. Interestingly, the short term interventions which provided intervention adherence data (beyond the percentage of youth returning for follow-up measures) report adherence rates ranging from 86-91% while attendance adherence ranged from 41.5-56% in interventions lasting six months or longer (Table C 5). Clearly, low adherence can be a major confounder in longer term intervention studies and have important implications for real world policy and programming. Although our adherence rates are similarly low, we have been consistently implementing measures to improve adherence to both attendance and intensity over the course of the trial. Specifically, we note that approaching three months into the trial attendance drops from approximately 58% to just over 40% (Figure C 5). This three month window at the end of the trial is critical, as any metabolic benefit achieved from the first three months of participation can diminish toward baseline in this time period (Chang, Liu et al. 2008). As a result we are presently implementing new measures to enhance motivation and adherence throughout the trial, recognizing that specific effort needs to be directed at maintaining motivation from the halfway point to trial completion (Supplement C 2). The majority of the adherence strategies detailed in the supplement were developed from informal discussion and observation of training patterns with the youth who

were included in the present analysis as well as from structured trainer meetings.

Limitations

Aside from the issue of adherence which is common to trials of this nature and duration, our study may be limited by the wide range of pubertal stage of participants at enrolment. To minimize the effect of these factors, self reported Tanner stage data is being collected, and age and pubertal stage will be used as covariates in the final analyses. Additionally, our sample size is far greater than previous related interventions which will allow for a certain level of variability. Behaviour compensation for both leisure time physical activity and energy intake may also occur with exercise trials in youth, as has been demonstrated in adults (Whybrow, Hughes et al. 2008). We will attempt to control for changes in energy intake by comparing pre and post nutritional assessments using a food frequency questionnaire (Rockett, Wolf et al. 1995). Seven-day pedometer records will be used to assess changes in leisure time physical activity levels. Another potential confounder common to randomized controlled physical activity trials is that the control group likely will consist of youth who are more motivated to make lifestyle changes than the general population, and changes in physical activity in this group have the potential to mask intervention effects (Warren, Golley et al. 2007). We anticipate that the effect size of the intervention will be sufficient to overcome this limitation.

The POWER Trial was specifically designed as a community based inclusive

exercise intervention to increase its relevancy and enhance the opportunity for community adoption. The YMCA is a family oriented facility with branches across Winnipeg. Membership assistance programs ensure that families from all socioeconomic levels have equal accessibility. The POWER Trial was designed to provide insight into the physiologic relationship between exercise intensity, insulin sensitivity and intrahepatic lipid. Upon completion we anticipate that it will also provide evidence and a template for an effective community based obesity management program.

Tables Study C.

Table C 1. Participant characteristics

Variable	*Low intensity*	*High intensity*	*Control*
n	15	18	15
Age	16.3 (5.1)	15.5 (1.8)	15.2 (2.1)
Sex (M/F)	4/11	2/16	5/10
Ethnicity (Cs/FNM/O)	12/2/1	16/2/0	9/4/2

Table C 2. Baseline and follow-up characteristics of POWER subjects

Variable	*Low Intensity*			*High Intensity*			*Control*		
	Baseline	*6 months*	Δ	*Baseline*	*6 months*	Δ	*Baseline*	*6 months*	Δ
Height (cm)	168.1 (8.3)	169.7* (8.5)	1.6 (1.4)	165.4 (6.6)	166.2† (6.0)	0.9 (1.6)	166.1 (7.6)	167.3† (7.7)	1.2 (1.9)
Mass (kg)	87.2 (19.0)	88.5 (20.6)	1.4 1.6)	86.5 (14.0)	87.3 (14.6)	0.8 (4.5)	86.5 (14.1)	88.1 (15.6)	1.6 (5.8)
BMI z-score‡	1.88 (0.47)	1.86 (0.52)	-0.02 (0.33)	1.93 (0.31)	1.86† (0.33)	-0.06 (0.15)	1.96 (0.48)	1.92 (0.52)	-0.03 (0.15)
Body fat (%)	37.7 (5.3)	37.0 (6.3)	-0.7 (2.7)	39.8 (3.6)	39.2 (3.7)	-0.5 (1.4)	38.1 (4.9)	37.6 (6.2)	-0.5 (2.0)
Lean mass (kg)**	52.1 (10.5)	54.3* (10.9)	2.2 (2.3)	49.8 (6.1)	50.9† (6.5)	1.1 (2.5)	50.9 (6.9)	52.5† (8.0)	1.6 (3.1)
Waist circumference (cm)	95.4 (13.2)	97.6 (16.0)	2.2 (10.5)	107.3 (12.1)	102.5 (20.4)	-4.8 (15.7)	103.8 (11.1)	106.5 (14.2)	2.7 (5.5)
Hip circumference (cm)	108.0 (10.3)	114.3 (22.2)	6.3 (16.6)	110.4 (8.5)	108.5 (18.7)	-1.8 (17.1)	109.9 (10.5)	108.3 (9.8)	-1.6 (5.1)
Total weekly steps (steps/day)	6685 (1946)	6307 (2565)	-378 (1271)	7007 (2365)	8070 (2321)	1063 (2766)	6524 (2371)	5958 (2374)	-567 (2766)
Weekday steps (steps/day)	6682 (2676)	7207 (2931)	525 (1349)	7313 (2387)	8476 (2305)	1163 (3170)	6436 (2435)	6220 (2809)	-215 (2450)
Weekend steps (steps/day)	6593 (1676)	4004 (2824)	-2589 (3456)	5277 (1563)	7017 (2772)	1740 (2381)	6035 (3586)	5798 (3929)	-237 (5906)

Repeated measures ANOVA
**significance <0.05
‡approaching significance

Paired t-test p value adjusted for multiple comparisons: p<0.017 is significant
* significantly different than baseline measure: p<0.017
†approaching significance:
†high intensity:
height p=0.03, BMI z-score p=0.09, fat free mass p=0.08,
weekend steps p=0.08
†control: height p=0.02, fat free mass p=0.06

Table C 3. Cardiometabolic characteristics at baseline and follow-up

Variable	*Low Intensity*			*High Intensity*			*Control*		
	Baseline	*6 months*	Δ	*Baseline*	*6 months*	Δ	*Baseline*	*6 months*	Δ
Insulin sensitivity	4.1 (2.9)	3.8 (2.4)	-0.3 (2.0)	3.9 (1.8)	4.1 (1.2)	0.3 (2.1)	3.0 (1.2)	4.1* (1.3)	1.1 (1.3)
Acute insulin response	698.6 (412.2)	711.5 (549.7)	12.9 (250)	629.4 (297.0)	586.1 (276.8)	-43.3 (310.9)	736.8 (457.1)	793.7 (496.8)	56.9 (323.8)
Disposition index	2560.6 (2491.3)	2069.2 (1207.9)	-491.3 (1905)	2270.7 (1226.7)	2274.8 (1196.1)	4.1 (1366.0)	1890.7 (663.6)	2884.4* (1435.0)	993.8 (1041.4)
Fasting insulin	172.0 (102.6)	102.3 (76.2)	-69.4 (175.8)	107.3 (73.3)	83.5† (34.5)	-23.8 (53.3)	157.1 (183.7)	112.2 (52.9)	-44.9 (184.2)
Fasting glucose	4.6 (0.5)	4.5 (0.2)	-0.1 (0.5)	4.7 (0.4)	4.6 (0.4)	-0.1 (0.4)	4.8 (0.7)	4.8 (0.4)	0.0 (0.5)
Intrahepatic lipid (%fat/water)	8.2 (10.7)	7.8 (11.2)	-0.4 (4.3)	5.2 (4.9)	4.9 (3.6)	-0.3 (2.9)	5.7 (5.3)	6.3 (8.1)	0.6 (3.3)
AST	24.6 (12.1)	22.9 (10.8)	-1.6 (11.1)	20.9 (6.3)	19.9 (7.2)	-1.0 (7.7)	28.5 (21.4)	27.4 (21.7)	-1.1 (8.9)

Variable	*Low Intensity*			*High Intensity*			*Control*		
(Table C3 continued)	*Baseline*	*6 months*	Δ	*Baseline*	*6 months*	Δ	*Baseline*	*6 months*	Δ
ALT	30.7 (28.5)	22.0 (18.6)	-8.7 (23.2)	17.1 (5.7)	15.5 (4.1)	-1.6 (5.9)	29.3 (30.3)	26.1 (27.5)	-3.1 (7.0)
Cholesterol	4.2 (0.7)	3.8* (0.6)	-0.3 (0.4)	4.5 (0.8)	4.1* (0.6)	-0.4 (0.6)	4.2 (1.1)	3.9† (1.2)	-0.2 (1.4)
LDL	2.3 (0.6)	2.0* (0.6)	-0.4 (0.4)	2.7 (0.7)	2.4† (0.5)	-0.3 (0.5)	2.5 (0.7)	2.5 (1.0)	-0.1 (0.4)
HDL	1.22 (0.31)	1.16 (0.34)	-0.05 (0.26)	1.29 (0.35)	1.15* (0.28)	-0.14 (0.18)	1.11 (0.27)	1.06 (0.27)	-0.04 (0.16)
TG	1.3 (1.0)	1.5† (1.2)	0.2 (0.4)	1.1 (0.4)	1.2 (0.5)	0.1 (0.5)	1.2 (0.6)	1.0 (0.4)	-0.1 (0.3)
SBP	111.1 (10.4)	110.5 (10.5)	-0.6 (9.2)	117.6 (9.4)	116.4 (11.5)	-1.2 (11.2)	116.1 (10.7)	112.6 (13.1)	-3.5 (11.8)
DBP	62.6 (7.8)	70.1 (9.7)	8.4 (11.7)	67.7 (7.1)	67.5 (9.0)	0.7 (10.9)	63.1 (8.5)	67.6 (8.1)	3.1 (8.5)

Paired t-testing p value adjusted for multiple comparisons: $p<0.017$ is significant
* significantly different than baseline measure: $p<0.017$
Approaching significance:
†low intensity: triglycerides $p=0.02$
†high intensity: fasting insulin $p=0.08$, LDL $p=0.03$
†control: cholesterol $p=0.05$

Table C 4. Fitness baseline measures and change at follow-up

Variable	*Low intensity*	Δ	*High intensity*	Δ	*Control*	Δ
Max HR	189.7 (8.5)	1.8 (8.4)	187.4 (9.8)	2.0 (10.3)	191.2 (11.2)	1.9 (5.6)
VO_2 (L/min)	2.2 (0.4)	0.2 (0.3)	2.1 (0.3)	0.1 (0.2)	2.2 (0.4)	0.1 (0.3)
VO_2 (ml/kg/min)	26.2 (4.2)	1.5 (3.8)	25.4 (4.1)	-0.6 (5.6)	25.6 (4.9)	-0.5 (2.4)
VO_2 (ml/kgFFM/min)	44.0 (3.6)	1.1 (4.0)	43.5 (5.5)	1.2 (5.2)	42.8 (6.6)	-0.8 (5.2)
Workload (watts)	166.6 (36.1)	-12.0 (28.5)	169.5 (27.7)	11.2 (49.2)	163.6 (40.7)	-2.2 (19.2)
RPE (/20)	17.4 (2.3)	-	16.7 (2.7)	-	17.4 (1.9)	-
RER	1.19 (0.08)	-	1.18 (0.07)	-	1.17 (0.06)	-

HR: heart rate
RPE: Rate of perceived exertion
RER: Respiratory exchange ratio

Table C 5. Reported adherence rates for physical activity and insulin sensitivity interventions.

Reference	*Trial duration*	*Adherence details*
Trial duration <6 months		
Van der Heijden et al (van der Heijden, Wang et al. 2010)	12 weeks	91% adherence to prescribed intervention
Farpour-Lambert et al (Farpour-Lambert, Aggoun et al. 2009)	3 months	86% of youth attended at the prescribed frequency
Nassis et al (Nassis, Papantakou et al. 2005)	12 weeks	90% of youth returned for majority of follow-up measures *No specific data on adherence to prescribed exercise dose
Shaibi	4 months	79% returned for follow-up testing *No specific data on adherence to prescribed exercise dose
Trial duration ≥6 months		
Tsang et al (Tsang, Kohn et al. 2009)	6 months	50.1% attendance adherence in the exercise group, 41.5% adherence in the control
Kang et al (Kang, Gutin et al. 2002)	8 months	51% and 56% adherence in the moderate and high intensity groups 76% and 68% of youth in moderate and high groups attended >40% of sessions
Kelishadi et al (Kelishadi, Hashemipour et al. 2008)	6 months	87% completed the trial and returned for follow-up measures *No specific data on adherence to prescribed exercise dose
Chang et al (Chang, Liu et al. 2008)	8 months	76% from intervention returned for follow-up measures, 75% from control *No specific data on adherence to prescribed exercise dose

Figures Study C

Figure C 1. Flow of participant from Study B to Study C (POWER Trial).

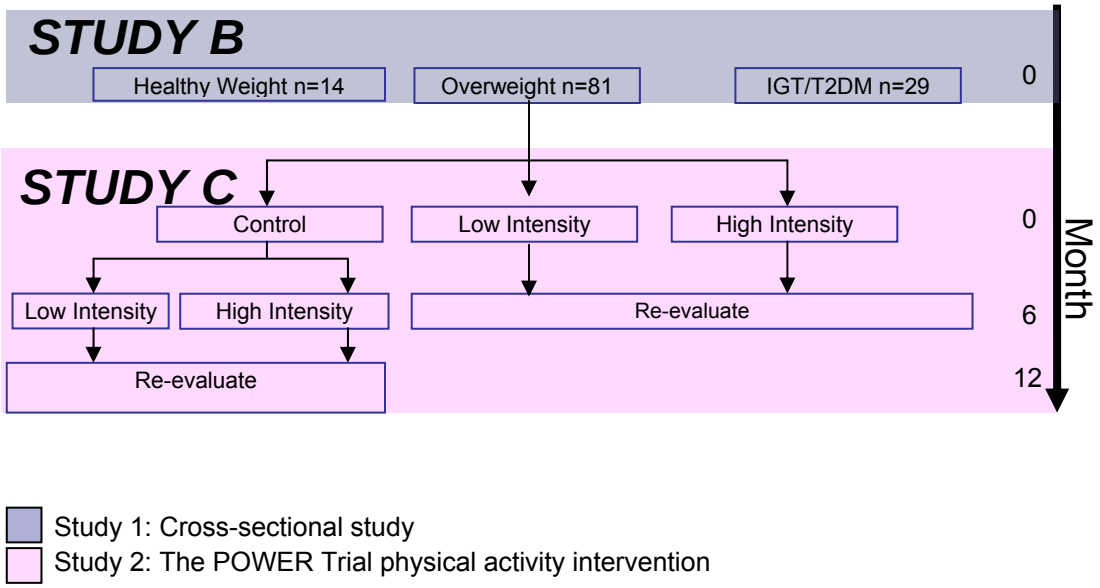
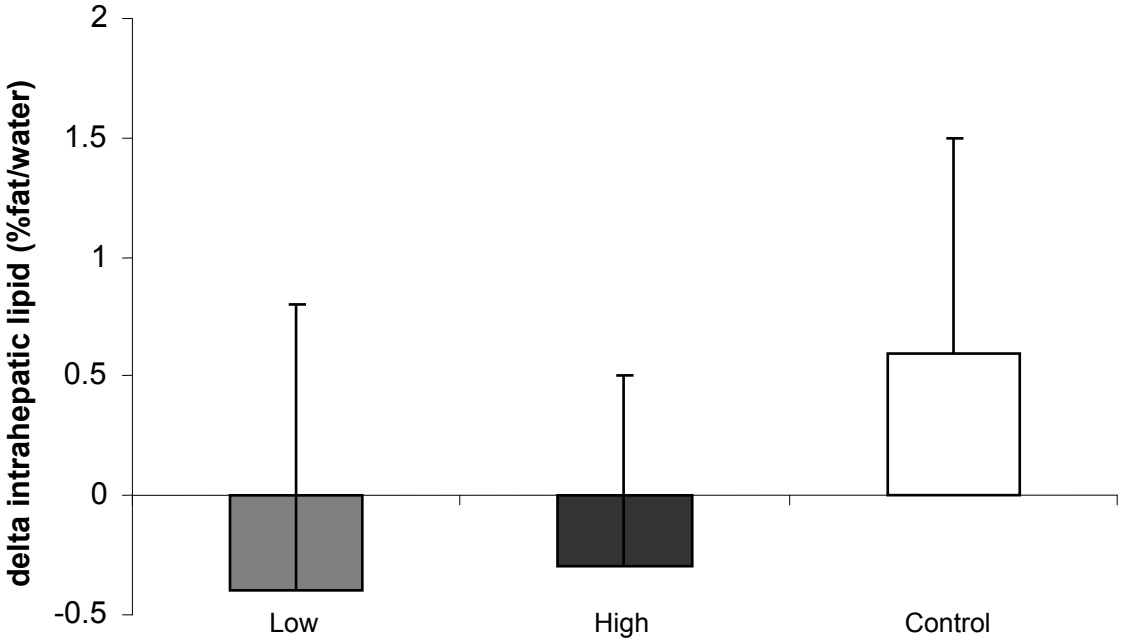
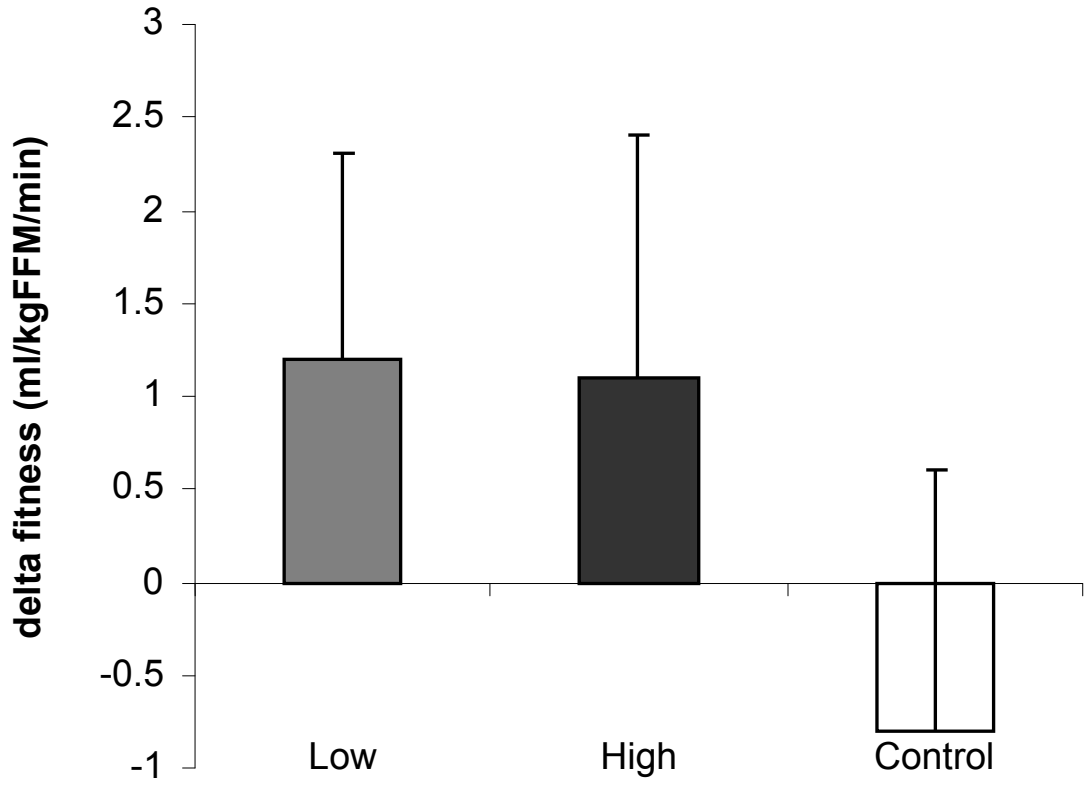


Figure C 2. Change in intrahepatic lipid levels (%) from baseline to 6-month follow-up.



Data presented as mean ± standard error

Figure C 3. Change in Fitness (ml/kgFFM/min) from baseline to 6-month follow-up.



Data presented as mean ± standard error

Figure C 4. Trend toward decreasing levels of intrahepatic lipid with improvement in fitness.

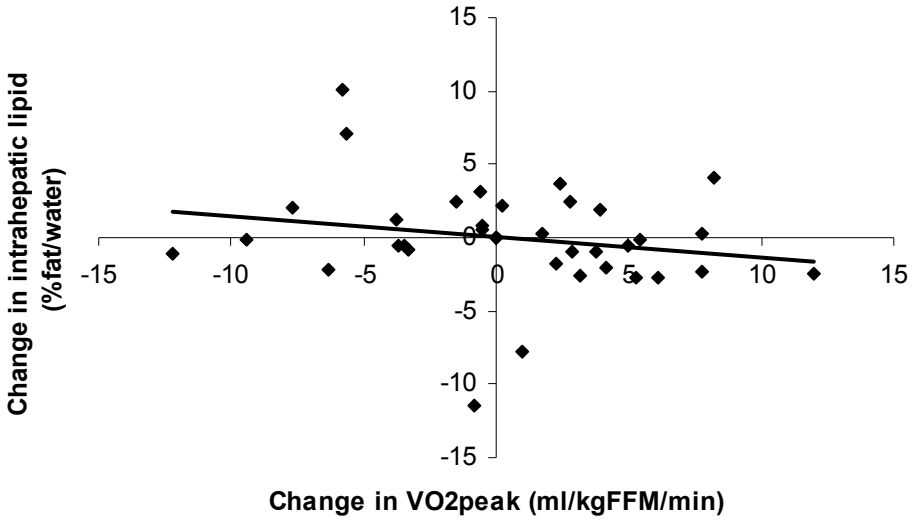
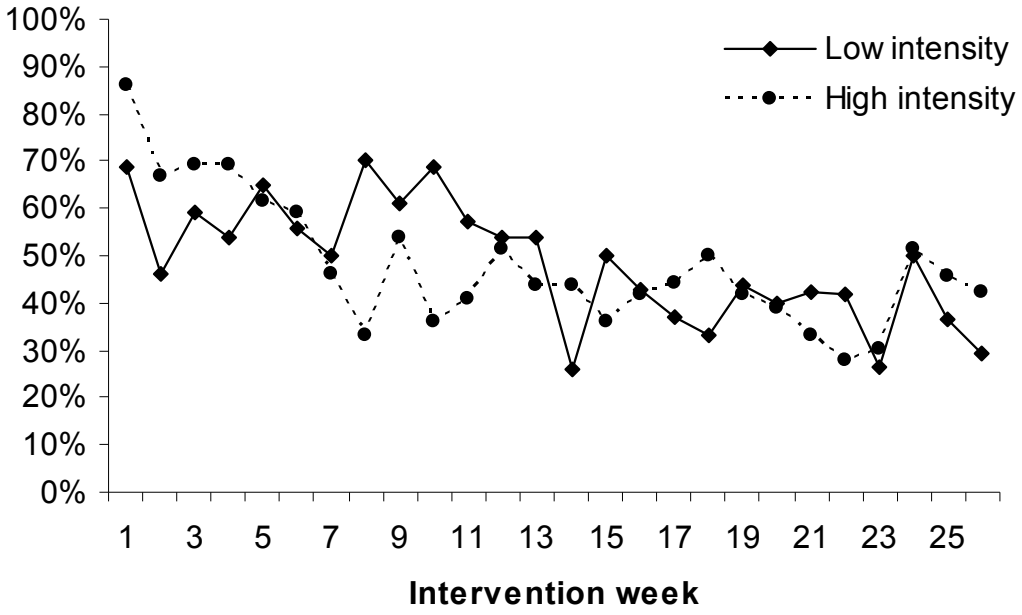


Figure C 5. Weekly attendance adherence by group.



Attendance adherence defined as:

(number of sessions attended per week / 3)*100.

Supplements Study C.

Supplement C 1. POWER Trial Contract

Welcome to the POWER Trial! This form explains what will be expected of you during the next six months. You will be asked to sign this form to indicate that you understand and agree to the guidelines and expectations of the POWER Trial.

Run-in Phase:
To be eligible for the full POWER Trial, you need to complete 4 supervised training sessions within a 2 week period. Your run-in phase starts on: _____, and must be completed by: _____.

Once you successfully complete your run-in phase, you will be randomized to either:
1. low intensity exercise
2. high intensity exercise
3. control group

Every one who completes the run-in phase receives a POWER Trial hoodie, a logbook with study information and invitations to holiday events. You will also be granted access to our website www.thepowertrial.com.

If you are **randomized to control**, continue to participate in your usual physical activities. Study staff will contact you to invite you to fun events the study puts on. After 6 months you have the option of joining the exercise group.

If you are **randomized to low or high intensity exercise group**, the study staff will purchase your 6 month YMCA pass, and together you will establish your training schedule (days / location) for the next 6 months. You will be provided with a heart rate monitor to track your exercise during the trial. You will be booked for one additional session in the lab to exercise on the treadmill with the metabolic cart for an "energy expenditure test". At this time you will also agree on a 6-month training goal.

In the exercise groups you are expected to:
1. Attend the YMCA 3x/week
2. Bring your heart rate monitor and logbook to each workout session.
3. Wear appropriate clothes and footwear to exercise in (indoor/outdoor as appropriate).
4. Contact study staff in advance if you will miss a scheduled exercise session.
5. Record your exercise data in your logbook.

You will be shown how to use your HR monitor and logbook to record your exercise.

Missed sessions:
It is very important both for achieving your goals and for the outcome of this study that you attend all scheduled workouts.
If you miss one exercise session you will be contacted by a trainer to arrange a good time to make up the session.
If you miss several sessions, we will discuss attendance strategies with you and your parents in person or over the phone.
If you still are not attending sessions regularly, we will have a meeting with you, your family and study staff to develop a plan to get your workouts back on track.

As a parent/guardian of a teen in the POWER Trial, you are expected to:

1. Support your child's participation in the study by providing transportation, a bus schedule, or simply encouraging your child to attend all the training sessions
2. Communicate with study staff if your child is going to miss a session PRIOR to the session date
3. Be available for regular contact from your child's trainer for progress updates

Statement of Agreement

We have read the guidelines and expectations and agree to the conditions as listed. We have had the opportunity to discuss the POWER Trial with study staff.

Signatures:

_____	_____	_____
(participant signature)	**(participant name printed)**	**(date)**
_____	_____	_____
(parent/guardian signature)	**(parent/guardian printed)**	**(date)**
_____	_____	_____
(witness signature)	**(witness name printed)**	**(date)**

Supplement C 2. Strategies to promote adherence

Strategy	*Description*
Run-in phase	Youth are required to attend 4 supervised sessions at the YMCA within 2 weeks prior to randomization into the trial
Team hoodie	Each youth was provided with a POWER hoodie at randomization Hoodie was designed by a study participant
Contract (Appendix C1)	Parents and youth signed contract at randomization outlining expectations of trial Collected data from trainers
Training coordinator	Monitored adherence (attendance and intensity) and provided feedback to trainers Contacted youth with low adherence to identify and address barriers to participation
Goal setting	Participants were encouraged to develop a short term and long term activity based goal (i.e. distance or time to run without stopping)
Consistent trainer	Based on feedback from participants, consistent trainers were provided at each YMCA
Friend involvement	Participants were encouraged to bring a friend to the YMCA to train with
Parents involved	Parents were offered training advice if interested, and encouraged to exercise while youth trained
"Fun" days every 1-2 weeks	Ultimate, soccer or easy day (tailored to preference of group)
Races	MB Marathon relay, Run for the Cure, Santa Shuffle to increase motivation and facilitate goal setting
Team events	Christmas parties (bowling), Halloween ultimate party, summer BBQ and games, corn maze, Teddy Bear Picnic volunteering
Website www.thepowertrial.com	A resource to parents and participants Training schedules / changes and events posted Links to pertinent websites
Transportation	Bus tickets provided to participants as needed for transportation to and from training sessions
Trainer support	Weekly trainer meetings were held to strategize and address issues in a timely manner (non-attendance) Trainer retreat February 2010
Midway participant feedback (in development)	Feedback to be provided to youth and parents at 3 months detailing progress, adherence and expectations for the remaining 3 months

Chapter 6

General Discussion

GENERAL DISCUSSION

Overview of the results

Exercise is frequently recommended as the front-line therapy for obesity, insulin resistance and type 2 diabetes in both adults and youth (Lau, Douketis et al. 2007; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008; Rosenbloom, Silverstein et al. 2008). Importantly, physical activity is also recognized for its key role in obesity and type 2 diabetes prevention. Accordingly, as recently reviewed in the Canadian Journal of Public Health, a number of physical activity initiatives in Canada have been implemented within the last several years (Tremblay 2007). Ten major obesity-prevention related initiatives were detailed in this review, including initiation of the Children's Fitness Tax Credit, re-implementation of ParticipACTION and the release of the 2006 Canadian Clinical Practice Guidelines on the Management and Prevention of Obesity in Adults and Children (Lau, Douketis et al. 2007). These wide-reaching programs, initiatives and guidelines are promising as they have the potential to increase physical activity participation at the community level, while providing clinicians with standardized management algorithms for those already overweight or obese. Ongoing population-based physical activity monitoring surveys such as those conducted by the Canadian Fitness and Lifestyle Research Institute (Canadian Fitness and Lifestyle Research Institute 2007) and program specific evaluation such as that designed for ParticipACTION

(Tremblay and Craig 2009) will help determine the effectiveness of these and other initiatives for increasing physical activity participation in adults and youth. A potential downfall of population-based strategies to increase physical activity however is that they may have preferential uptake by families that are already active. As we gain an appreciation for the metabolic consequences of youth-onset obesity, there is a need to determine the optimal dose and mode of delivery for physical activity interventions specifically tailored toward youth who are at risk for comorbidities related to obesity or physical inactivity.

Fortunately, with the progression of science and technology (Esliger and Tremblay 2007) there have been major advances in our understanding of the relationship between physical activity variables and the determinants of insulin resistance. Specifically, recent investigations using objective measures of physical activity have highlighted the importance of fitness and moderate to vigorous intensity physical activity as protective factors against excess adiposity and insulin resistance (Kasa-Vubu, Lee et al. 2005; Benson, Torode et al. 2006; Morinder, Larsson et al. 2009). However we still do not fully understand the mediating factors between cardiorespiratory fitness and insulin resistance in youth, and further, there is a lack of effective evidence-based programs for the prevention and management of type 2 diabetes in youth. This thesis has begun to address these issues in an attempt to allow clinicians and policy makers alike to advocate for and implement targeted evidence-based physical activity

programming in the clinic and community.

Study A examined the use of lifestyle monotherapy using 10 years of data from the largest clinical cohort of youth with type 2 diabetes, demonstrating that > 50% of youth newly diagnosed with type 2 diabetes and an HbA_{1c} < 9.0% can maintain target glycemia for a minimum of one year without pharmacologic intervention. This information can immediately be used in clinical decision making, and for certain youth, may delay or reduce the use of pharmacologic agents for glycemic control for which we do not know the long term effects. Previous research on the use of lifestyle monotherapy for glycemic management in youth with type 2 diabetes has reported disappointingly low success rates (Grinstein, Muzumdar et al. 2003; Reinehr, Schober et al. 2008). However, these studies examined the success rate with lifestyle therapy in the whole clinical cohort rather than specifically in youth who were appropriate for this type of treatment. According to the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines (Rosenbloom, Silverstein et al. 2009), youth who are "asymptomatic" at diagnosis of type 2 diabetes (*defined as* HbA_{1c} *< 9%, absence of ketoacidosis, glucose < 14mmol/L*) are eligible for treatment with diet and exercise alone, while those with HbA_{1c} ≥ 9% or who are "symptomatic" should be managed with lifestyle *plus* pharmacology. Presenting clinical success rates of lifestyle monotherapy for a cohort which includes youth with an HbA_{1c} ≥ 9% substantially underestimates the efficacy of lifestyle monotherapy. This has

the potential to reduce clinical confidence in lifestyle treatment and may preclude the clinician from viewing it as a viable treatment option. We have provided evidence that over 50% of youth with new-onset type 2 diabetes and an HbA_{1c} < 9% can successfully achieve and maintain target glycemic control for at least one year following diagnosis. Youth who were successful with lifestyle monotherapy appeared to be in an earlier stage of metabolic decompensation as indicated by higher fasting insulin levels, and a lower mean initial HbA_{1c}. This allows clinicians to identify youth with type 2 diabetes who may benefit from standard lifestyle advice. These data could be used to develop an algorithm to target youth that are more likely to respond to an intensive lifestyle-based management program. Finally, the evidence presented within Study A justifies a 'lifestyle only' arm in future randomized controlled trials of glycemic control for youth with type 2 diabetes, which is the next logical step toward evidence based recommendations for lifestyle management of glycemic control and / or complications for youth with type 2 diabetes.

From a prevention perspective, Study B examined the relationship between cardiorespiratory fitness and conventional and novel risk factors for type 2 diabetes. Fitness was 35% lower in youth with impaired glucose tolerance / type 2 diabetes compared with non-overweight normoglycemic controls and 12% lower than overweight controls. Similarly, physical activity measured by pedometry was approximately 45% and 30% lower in youth with impaired

glucose tolerance / type 2 diabetes versus non-overweight and overweight controls respectively. Two recent studies have similarly reported reduced fitness in small samples of youth with type 2 diabetes relative to their overweight normoglycemic peers (Shaibi, Faulkner et al. 2008; Nadeau, Zeitler et al. 2009). Shaibi and colleagues compared fitness and self-reported physical activity levels between overweight adolescent males with and without type 2 diabetes (n=13 in each group) (Shaibi, Faulkner et al. 2008). Males with type 2 diabetes reported roughly 60% less moderate to vigorous physical activity time than overweight controls ($p<0.05$); and fitness levels were 17% lower in youth with type 2 diabetes. In line with these findings, Nadeau and colleagues also found fitness to be almost 20% lower in youth with type 2 diabetes compared with overweight controls, and 46% lower than lean youth. These results are in agreement with adult data that has found fitness levels to be 20-25% lower in adults with type 2 diabetes compared with normoglycemic peers (McGavock, Eves et al. 2004).

In contrast to our results and those found by Shaibi et al., Nadeau and colleagues found that youth with type 2 diabetes self-reported the same level of physical activity (metabolic equivalents; METS) as lean youth, which was almost 10% higher than that reported by overweight controls (non-significant). This discrepancy may be due to the limitations of subjective measurement of physical activity (Prince, Adamo et al. 2008; Adamo, Prince et al. 2009), the inclusion of all intensities of physical activity (in contrast to only moderate-vigorous activity as

measured by Shaibi et al), or a combination of these factors.

Our data extend the findings from these two studies by including an objective measure of physical activity, as well as providing evidence for a relationship between fitness and risk factors for type 2 diabetes, in particular insulin sensitivity and intrahepatic lipid content. Interestingly, while fitness was associated with both insulin sensitivity and intrahepatic lipid content, it was only intrahepatic lipid that predicted insulin sensitivity in regression analysis. This is consistent with recent adult data which suggest that fitness may be associated with insulin sensitivity through an interaction with intrahepatic lipid content (Haufe, Engeli et al. 2010). Haufe and colleagues performed a cross-sectional study of 138 sedentary overweight adults; the only study other than ours that we could identify which assessed the relationship between fitness, insulin sensitivity and intrahepatic lipid content. Subjects underwent a 2-hour OGTT from which insulin resistance (HOMA-IR) and insulin sensitivity index were derived. Peak oxygen uptake was measured from a cycle ergometer test to exhaustion and visceral fat and intrahepatic lipid content were measured using MRI / ^{1}H-MRS. Haufe and colleagues found that fitness was positively and significantly associated with insulin sensitivity ($r=0.32$, $p<0.05$), an effect size similar to that reported by our group and others (Kasa-Vubu, Lee et al. 2005; Allen, Nemeth et al. 2007; Eisenmann, DuBose et al. 2007). However, this association was no longer significant after adjusting for intrahepatic lipid content ($r=0.16$, non-significant).

Our findings were in agreements with these, as intrahepatic lipid content was a significant predictor of insulin sensitivity independent of fitness, sex, ethnicity and percent body fat.

In the absence of measures of fitness; Klein, Fabbrini and associates have elegantly demonstrated in adults and adolescents that high levels of intrahepatic lipid are associated with impaired insulin action in multiple target tissues, including skeletal muscle, adipose tissue and the liver; independent of measures of adiposity such as BMI, body fat and even visceral fat (Deivanayagam, Mohammed et al. 2008; Korenblat, Fabbrini et al. 2008; Fabbrini, Magkos et al. 2009).

Importantly, in both adults and adolescents, weight loss achieved through diet and exercise can reduce intrahepatic lipid levels by up to 60%, suggesting a major role for lifestyle in reducing the metabolic consequences associated with steatosis (Wang, Liang et al. 2008; Vitola, Deivanayagam et al. 2009). To date however, only the one previously discussed study by van der Heijden and colleagues has examined the effect of exercise alone on hepatic lipid levels and insulin sensitivity in adolescents (van der Heijden, Wang et al. 2010). This study specifically examined the effect of high intensity exercise on metabolic risk in youth, therefore the intensity of physical activity which is most effective for improving insulin sensitivity and intrahepatic lipid levels has yet to be established. Accordingly, Study C presented preliminary results from a randomized controlled

trial testing the effectiveness of low (40-55%HRR) versus high (70-85%HRR) intensity exercise to reduce intrahepatic lipid and improve insulin sensitivity in youth at high risk for type 2 diabetes.

Previous cross-sectional research in adults has demonstrated a significant dose-response association between moderate and vigorous intensity physical activity accumulation and insulin sensitivity (Mayer-Davis, D'Agostino et al. 1998; Balkau, Mhamdi et al. 2008). Although total energy expenditure (i.e. from all intensities of activity) modified this relationship in the Insulin Resistance and Atherosclerosis Study, the proportion of time that was spent in vigorous activity was low (< 2% of the day) (Mayer-Davis, D'Agostino et al. 1998) which may greatly underestimate the effect of time spent in vigorous intensity activity.

The intensities used in the POWER Trial are based on previous trials evaluating the effects of exercise intensity in adults (Kang, Robertson et al. 1996; Kraus, Torgan et al. 2001; DiPietro, Dziura et al. 2006; Tjonna, Lee et al. 2008; Hansen, Dendale et al. 2009) and one study which examined this relationship in youth (Kang, Gutin et al. 2002).

Adult participants of 'Studies of a targeted risk reduction intervention through defined exercise' (STRRIDE) were randomized to one of three groups; i) low amount, moderate intensity (40-55% VO_{2peak}), ii) low amount, vigorous intensity (65-80% VO_{2peak}) and iii) high amount, vigorous intensity (65-80% VO_{2peak}). The high amount, vigorous intensity group demonstrated superior improvements in

body composition and reduction in acute insulin response to glucose challenge (Slentz, Duscha et al. 2004; Slentz, Tanner et al. 2009), potentially indicating that exercise duration or total caloric expenditure was a major mediator of change in these studies. Interestingly, the low amount, moderate intensity group had the greatest improvement in insulin sensitivity.

Tjonna and colleagues completed a similar study in subjects who had multiple risk factors for type 2 diabetes / cardiovascular disease (termed 'metabolic syndrome'). Four months of training at high intensity (90% peak HR) resulted in a greater reduction in cardiometabolic risk factors (5.9 risk factors reduced to 4.0 risk factors) than training at a lower intensity (70% peak HR; 5.7 reduced to 5 risk factors). This is in agreement with findings from DiPietro and colleagues, who completed a nine-month multi-armed randomized controlled intervention testing different exercise intensities in older (>60 years) non-obese females, of whom approximately half had impaired glucose tolerance. Those who were randomized to the high intensity arm (80% VO_{2peak}) had superior improvements in glucose utilization and suppression of lipolysis compared with those who trained at low intensity (60% VO_{2peak}) (DiPietro, Dziura et al. 2006).

In contrast, Hansen and colleagues were unable to demonstrate a difference between six months of low versus high intensity training in adult men with type 2 diabetes (Hansen, Dendale et al. 2009). Overall training intensities were relatively low in this study however (low intensity: 50% VO_{2peak}, HR 105±3 bpm

versus high intensity: 70% $VO_{2peak,}$ HR 118±3bpm) which may have contributed to null findings.

Kang and colleagues are the only group to have completed a study comparing the effect of exercise intensity on risk for type 2 diabetes in adolescents (Kang, Gutin et al. 2002). While exercise in general resulted in reduction of risk factors for type 2 diabetes; poor adherence to prescribed exercise intensity resulted in an inability to delineate the specific effects of exercise intensity on insulin sensitivity (Kang, Gutin et al. 2002). At the time of the POWER Trial interim analysis, the high intensity group on average did not meet the prescribed training intensity, resulting in a smaller than anticipated difference in intensity between the high and low intensity arms (65 versus 54% of HRR). As a result, we are implementing multiple measures to consistently improve adherence to the prescribed intensity within the POWER Trial to maximize our ability to detect differences between the training arms.

As there have been only a few studies which attempted rigorous evaluation of the impact of exercise intensity on metabolic risk in adults (Kraus, Torgan et al. 2001; Tjonna, Lee et al. 2008; Hansen, Dendale et al. 2009), and only one identified study in youth to date (Kang, Gutin et al. 2002), further research is necessary to determine the optimal training intensity, as well as the duration, frequency and type of physical activity to reduce the risk for type 2 diabetes in adolescents. Interim results from the POWER Trial demonstrate a promising trend for

reductions in intrahepatic lipid and other risk factors for type 2 diabetes including cardiometabolic risk factors and waist circumference in the intervention groups. A major strength of the POWER Trial is its practicality and potential for translation into community programming.

Future directions

Despite mounting evidence, further research is still required to determine the effect of exercise alone on risk for type 2 diabetes (Orozco, Buchleitner et al. 2008). Accordingly, within this thesis, physical activity and fitness were primarily evaluated as lifestyle factors that can be used to prevent, delay or manage type 2 diabetes in youth. However it is clear that there are other key lifestyle factors, such as dietary practices and sleep that influence type 2 diabetes risk and management. While previous literature in youth support the role of physical activity and nutrition in the reduction of risk for type 2 diabetes (Monzavi, Dreimane et al. 2006; Savoye, Shaw et al. 2007); the 'ideal' lifestyle program has yet to be established. Future randomized controlled trials should be designed to evaluate the intricate relationship between physical activity dose, dietary composition / nutritional behaviours and diabetes risk. Other factors, such as sleep duration, sleep quality and sleep patterns as well as parental obesity and lifestyle behaviours are also important for metabolic regulation in adolescents (Tomoda, Kawatani et al. 2009) and should be examined or controlled for in future research.

Mixed methods designs should be strongly considered for future studies designed to evaluate the contextual factors that mediate the uptake and adherence to lifestyle behaviours among youth at risk for or diagnosed with type 2 diabetes. Poor adherence to lifestyle interventions is systemic, affecting both research (Kang, Gutin et al. 2002; Tsang, Kohn et al. 2009) and clinical practice (Zeller, Kirk et al. 2004; Kitscha, Brunet et al. 2009). In terms of knowledge translation, it is as important to understand the determinants of adherence and success with lifestyle interventions as it is to know the physiologic mechanisms underlying improved metabolic health.

Conclusion

Collectively, these three studies provide initial evidence that physical activity and fitness play a role in the prevention, identification and management of type 2 diabetes among youth. The results of this thesis emphasize the importance of programming, expertise and support for lifestyle interventions within the clinical realm and the community.

Appendices

Consent and Assent Forms

Appendix 1. Consent form Study A

Study Date:_____

Participant #: _____

PARTICIPANT INFORMATION AND CONSENT FORM

UNIVERSITY OF MANITOBA

STUDY TITLE: "Lifestyle characteristics of youth onset type 2 diabetes"

PROTOCOL #:

INVESTIGATORS:

Jonathan McGavock, PhD	Pediatrics	480-1359
Heather Dean, MD	Pediatrics	787-7435
Elizabeth Sellers, MD	Pediatrics	787-7435
Kristy Wittmeier, PT		789-3591

You are being asked to participate in a research study looking at the physical activity levels and nutritional habits of youth with type 2 diabetes. Researchers would like to know what types of lifestyle changes are best for controlling type 2 diabetes in youth. Before you agree to participate we will also require that your parent or guardian consent to your participation. Please take your time to review this consent form with your parent or guardian and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your parents, friends, family or your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Purpose of Study

Physical activity and healthy eating are important factors for managing type 2 diabetes. We know that physical activity and healthy eating can reduce blood sugar, but there is little information about how much activity or what type of dietary changes are best for youth with type 2 diabetes. If you agree to participate in this study, we will review your medical chart and ask you to complete a survey on your physical activity participation, and eating habits before and after being diagnosed with type 2 diabetes.

Am I Eligible to Participate?

You are eligible to participate if you have been diagnosed with type 2 diabetes before the age of 18, and have been able to control your blood sugar without using medication (for example, insulin). You are still eligible to participate if you have used medications for a brief amount of time in the past.

The study is purely voluntary and if you decide not to participate or withdraw, your normal medical care will not be affected in any way.

Study procedures

The primary goal of this study is to see what types of changes are related to successful management of type 2 diabetes. If you agree to participate, you will be asked to complete a short survey about your physical activity participation and eating habits. The researchers and your parent(s) may help you complete the survey. You will be asked to compare your physical activity and eating habits before and after you were diagnosed with diabetes. If you have made changes in these habits, you will be asked questions about what helped you make and keep those changes.

We will also look at your clinic chart to see how your body responded to these changes. We will look at how you have grown, and how your blood tests have changed since your diagnosis. We will also look at what type of education and suggestions you were given by your doctor and diabetes educators.

Participation in the study will take about 30 minutes and can be completed during your regular clinic visit.

The researcher may decide to take you off this study if you become uncomfortable with any of the questions that you are being asked. *You can withdraw from the study at any time, however if you decide to stop participating, we encourage you to talk to the study staff first.*

Risks and Discomforts

Survey: Some people are uncomfortable answering questions about their physical activity participation and eating habits. You do not have to answer any questions that you don't want to. You can ask for help to understand any questions that do not make sense to you. Your parent or guardian can

be present if you would like.

Chart Review: There are no risks associated with the chart review.

How you can help reduce risks:

During your participation in this study, you can reduce risk by asking questions about anything you do not understand. You can also:

- Talk to a family member or a friend, or your doctor about your participation in this research.
- Carry information about the research in your purse or wallet.

POSSIBLE BENEFITS

Benefit to you: There is no guarantee that you will directly benefit from participation in this research. You may receive additional information about physical activity and nutrition if you are interested. It will not cost you anything to participate in the study. You will also receive a summary of the findings of this research once the study is finished.

Benefit to youth who are at risk for or currently have type 2 diabetes: There are a growing number of youth who are considered at risk for type 2 diabetes and doctors need more information regarding risk factors that will help them prevent the disease. The information gathered in this study will help provide information regarding physical activity and nutrition changes that are helpful in managing type 2 diabetes in youth and may also help to prevent type 2 diabetes in youth who are at risk for this diagnosis.

Costs: All the procedures, which will be performed as part of this study, are provided at no cost to you or your parent/guardian. None of the study doctors, the University or the Manitoba Institute of Child health are receiving professional fees or personal financial support to conduct this study.

Payment for participation: There will be no payment for participation in this study.

Confidentiality

Information gathered in this research study may be published or presented in public forums; however your name and other identifying information will not be used or revealed. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. All study documents will refer to you with a number and your initials to protect your privacy

Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. The study doctors will need to have access to your medical records to keep track of any events that may occur during the study. This is a very common practice at the University and is done for the protection of youth participating in research.

Normally, only people directly involved with the research are allowed in the room when we complete the survey. Because the study takes place at the Health Sciences Center which is a clinical facility, people not involved in the research study may occasionally require access. All staff at the Health Sciences Centre are required to keep health information confidential, in accordance with the Health Information Act of Manitoba.

All data obtained during this study will be stored with an alpha-numerical code instead of your name. Only your file, which is kept in Dr. McGavock's office in a locked filing cabinet, will have information which relates your name to the code. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the University of Manitoba Health/Biomedical Research Ethics Board.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary and also depends upon your willingness to provide informed assent to participate. You may refuse to participate or you may withdraw from the study at any time. Your decision not to participate will not affect your care at this centre. If the study staff feels that it is in your best interest to withdraw from the study, we will remove you from the study without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Medical Care for Injury Related to the Study

In the case of injury or illness resulting from this study, necessary medical treatment will be available at no additional cost to you.

Please contact us if you would like any more information about the study.

Please let us know if you would like copies of any published scientific reports about the research project.

Questions

You are free to ask any questions that you may have about this investigation and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact the study doctor and the study staff:

Name	**Phone**
Jonathan McGavock, PhD	480-1359
Heather Dean, MD	787-7435
Elizabeth Sellers, MD	787-7435
Kristy Wittmeier PhD Candidate	789-3591

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at (204) 789-3389.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Dr. Elizabeth Sellers and or her study staff. I have had my questions answered by them in a language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship (such as employer, supervisor or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my health records that relate to this study by The University of Manitoba Research Ethics Board, for quality assurance purposes.

By signing this consent form, I have not waived any of my legal rights as a participant in a research study.

I agree to be contacted for future follow-up in relation to this study,
Yes _ No _

Participant signature_____ Date
_____

(day/month/year)
Participant printed name: _____

Parent/legal guardian's signature_____Date
_____

(day/month/year)
Parent/legal guardian's printed name: _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Printed Name: _____Date
_____

(day/month/year)
Signature: _____

"Role in the study: _____

Relationship (if any) to study team members:_____

Appendix 2: Assent form Study A

PARTICIPANT INFORMATION AND ASSENT FORM

STUDY TITLE:

"LIFESTYLE CHARACTERISTICS OF YOUTH ONSET TYPE 2 DIABETES"

Protocol #: H2008:094

INVESTIGATORS:

Jonathan McGavock, PhD	Pediatrics	480-1359
Heather Dean, MD	Pediatrics	787-7435
Elizabeth Sellers, MD	Pediatrics	787-7435
Kristy Wittmeier, PT, MSc	Study Staff/ Coordinator	789-3591

Why you are here?

The doctors want to tell you about a study about children with type 2 diabetes. They want to see if you would like to be in this study. This form tells you about the study. If there is anything you do not understand, please ask your parent, your guardian or the study staff.

Why are they doing this study?

They want to learn more about physical activity and eating habits in people who are controlling their type 2 diabetes without taking medication.

What will happen to you?

If you want to be in the study these things will happen:

1. The study will last about 30 minutes, and can be done during your

regular visit to the diabetes clinic.
2. You will be asked questions about your physical activity level and food choices. You will be asked to compare your activity and food choices before and after you were diagnosed with type 2 diabetes.
3. Your parent / guardian can help you answer the questions if you would like.
4. The researchers will also look at your clinic chart to see:
    a. what type of education and suggestions you were given by your doctor and diabetes educators, and
    b. how you have grown since your first visit to the clinic.

Will the study hurt?

You will not have to do any tests in this study that would hurt you.

With the survey, some people are uncomfortable answering questions about their physical activity participation and eating habits. You do not have to answer any questions that you don't want to. You can ask for help to understand any questions that do not make sense to you.

Will you get better if you are in the study?

This study will not make your diabetes go away. But the doctors might find out something that will help other children with diabetes in the future.

What if you have any questions?

You can ask questions any time, now or later. You can talk to the doctors, your family or study staff.

Who will know what I did in the study?

Any information you give to the study staff will be kept private. Your name will not be on any study paper and no one but the study staff and your doctor will know that it was you who was in the study.

Do you have to be in the study?

You do not have to be in the study. No one will be mad at you if you don't want to do this.
If you don't want to be in this study, just say so. We will also ask your parents if

they would like you to be in the study. Even if your parents want you to be in the study you can still say no. The doctor will still take care of your diabetes.
Even if you say yes now you can change your mind later. It's up to you.

Do you have any questions?

_____
_____

What questions do you have?

_____
_____
_____
_____

ASSENT

I want to take part in this study. I know I can change my mind at any time.

_____ Verbal assent given Yes ☐
Print name of child

Written assent if the child chooses to sign the assent.

_____ _____ _____
Signature of Child Age Date

I confirm that I have explained the study to the participant to the extent compatible with the participants understanding, and that the participant has agreed to be in the study.

_____ _____ _____
Printed name of Person obtaining assent | Signature of Person obtaining assent | Date

Appendix 3: Consent Form Study B

Study Date:_____

Participant #: _____

Participant Initials:_____

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: "Cardiorespiratory fitness, steatosis and insulin resistance in adolescents with and without type 2 diabetes"

PROTOCOL #: **B2006:091**

SPONSOR: **Manitoba Children's Hospital Foundation**

INVESTIGATORS:

Jonathan McGavock, PhD	Pediatrics	480-1359
Dean Kriellaars, PhD	Rehabilitation Medicine	787-3505
Heather Dean, MD	Pediatrics	787-7435
Elizabeth Sellers, MD	Pediatrics	787-7435
Lawrence Ryner, PhD	Radiology	984-7693
Phillip Gardiner, PhD	Physiology	474-7087

You are being asked to participate in a research study involving several visits to determine your risk for diabetes and your fitness. Before you agree to participate we will also require that your parent or guardian consent to your participation. Please take your time to review this consent form with your parent or guardian and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your parents, friends, family or your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Purpose of Study

Type 2 diabetes (formerly called adult diabetes) was once only found in older adults. Recently a growing number of teenagers have been diagnosed as having the adult form of diabetes. The reason for this premature onset of diabetes is not completely clear but we think it is related to differences in exercise capacity in children and the amount of fat stored in your muscle. If you agree to participate in

this study we will do two tests for diabetes risk, a test of exercise ability and an MRI of your muscle and liver. The MRI of the muscle is a new method to measure fat inside muscle and the liver without doing a biopsy and may provide information about your risk for diabetes.

Am I Eligible to Participate? We plan to study approximately 50 children with type 2 diabetes (Group 1) and 80 children without diabetes (Group 2).

For group 1, you are eligible to participate if you have been diagnosed with type 2 diabetes. *You can confirm with your doctor that you are eligible to participate.* **The study is purely voluntary and if you decide not to participate or withdraw, your normal medical care will not be affected in any way.**

For group 2, you must be healthy and able to perform an exercise test to measure your fitness. If you are participating in the Control group you must be healthy and have normal blood sugar. Screening by a physician is a requirement to participate. If you have been screened previously for one of our other MR studies, you may not need to have another form completed. Please check with the Principal Investigator at 480-1359, to ensure that you are eligible.

For both groups, all subjects who participate in this research study must be between 13 and 18 yrs of age and must pass a medical screen by his/her physician. If any of the following applies to you, you may not participate in the study:

1. You have metal objects inside your body. MRI may be dangerous for anyone with metal implants or metal objects inside their body.
2. You, in the opinion of the screening physician or investigators, have a medical condition that could be made worse by any stress associated with participation in a research protocol. These conditions include heart and circulatory problems, seizure disorders, anxiety disorders, and mental disorders.
3. You have claustrophobia
4. You are or may be pregnant.
5. You weigh more than 350 pounds.

Study procedures

Schedule of Study Visits

Visit	Purpose	Duration	Location	Contact #
#1	Screening for Diabetes *(Oral glucose tolerance Test)*, Exercise Stress Test and Dual energy x-ray absorptiometry (DEXA)	6.5 hours (week day)	Manitoba Institute of Child Health 5th Floor John Buhler Research Center 715 McDermott Ave	789-3968 or 480-1359
#2	Diabetes Test *(Frequently sampled glucose tolerance test)*, Arterial Stiffness measurement, MRI imaging of muscle and liver	6.5 hours (Saturday)		789-3968 or 480-1359

If you are diagnosed with type 2 diabetes or if your body weight falls within a certain range, you will qualify for the second part of this study, which involves a 6-month structured exercise training program at the University of Manitoba.

The primary goal of this study is to measure exercise tolerance, muscle fat and insulin sensitivity in adolescents with type 2 diabetes and compare these values to peers of the same age and gender that do not have diabetes (they will be called "*controls*").

What will I have to do if I participate?

Visit#1 - You will arrive at the John Buhler Research Centre at 8:00am. You cannot eat anything before arriving to the University and we ask that you not eat any food after 10 pm the night before. Someone will meet you at the front doors of the centre and escort you up to the lab. We will explain the study in detail and ask any questions you may have. After you and your parent/guardian have signed the consent form a nurse will insert a catheter (a needle and plastic tube) into a vein in your arm. You will have the option of using a special cream (called EMLA) used to numb the area where we will insert the needle. A small plastic tube will remain in your arm and be used to sample blood in small amounts during the test. We will use these samples to measure blood sugar levels, cholesterol, insulin, and the activity of energy producing cells (known as mitochondria) work in your system. After collecting a few samples you will consume a sugar drink. After finishing the drink, we will collect blood samples at 15,

30, 60, 90 and 120 minutes, from the tube that will remain in your arm. After the test we will provide a light breakfast than escort you to the exercise lab, where you will change into clothes appropriate for exercising

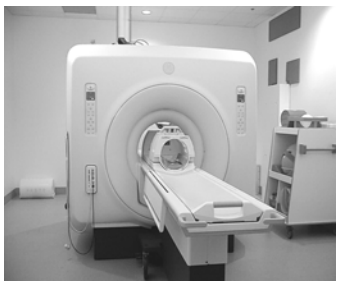
Once changed, we will escort you to quiet room where we will perform a scan of your body that measures the amount of muscle, fat and bone inside your body. This test takes approximately 10 minutes to perform and all you have to do lie still while a scan moves across your body. The machine takes an x-ray (picture) of your body that we can use to measure the size of your muscles. The amount of x-ray used in this test amounts to less than a regular chest x-ray and is similar to the amount of radiation a person is exposed to in the environment on a daily basis. Some researchers equate this to one commercial flight across Canada or living for one day in the city. **This test is completely safe and no needles are involved.**

The exercise test will be performed on a stationary bicycle. We will measure your heart rate and blood pressure throughout the test. We will also measure the air you exhale (breath out) during the exercise. This will give us an estimate of your current fitness level. After the first two minutes of exercise, we will increase the resistance against the pedals every two minutes until you are no longer able to pedal. When you can no longer keep pedaling we will stop the exercise test. You will be the one who decides when to stop. The study doctors will only encourage you to continue as long as you can. After monitoring you for a period of 20 minutes after the exercise, you will be free to go.

Visit #2 – Will likely take place on a Saturday as this is the best time to access the MRI machine at the Health Sciences Centre. You should fast overnight (i.e. not eat anything after 10 pm) and arrive to the lab between 7 and 7:30 in the morning. A member of our staff will meet you at the front door of the John Buhler Research Centre (715 McDermott ave.) We will escort you up the Institute for Child Health on the 5th floor, where a trained nurse will insert a catheter (i.e. small plastic tube) into a vein in your arm and another into your hand. One small tube will be used for collecting blood and the other will be used to inject a small amount of sugar into your body. We will start by taking three blood samples (-15 , -10 and -2 min) before injecting the sugar to measure blood sugar and cholesterol and at 8 am we will inject a sugar solution into one of the small tubes. The amount of sugar is very small and contains the same number of calories as an apple. This test will provide information about how the various systems in your body react to sugar, which will help us understand your risk for diabetes. After injecting glucose we will take blood samples at 2,3,4,5,6,8,10,14 and 19 min than we will inject a very small amount of

insulin to help return your blood sugar to normal levels (the amount injected will be a small fraction of the amount of insulin a child with diabetes would inject to control their blood sugar). After this injection we will take blood samples at 22,25,26,30,40,50,70,100,140 and 180 min. The amount of blood removed for each sample is no bigger than a teaspoon and the total amount is less than half of a small lunch sized (250 mL) juice box. During the blood sampling one of the research assistants will make repeated measurements of the pressure in a blood vessel in your wrist and your neck. This test does not involve a needle. Instead we will place a small metal device the size of a pen against your skin. This device will estimate the pressure in your blood vessel and provide us with information about the stiffness of your blood vessels. You will not experience any pain or discomfort during the measurements. We will make the measurements every 15 minutes during the test. After this test we will provide a light breakfast and escort you to the MRI centre in the Health Sciences Centre.

The MRI will take approximately 1 hour and all you have to do is lie still and listen to music. ***This test is completely non-invasive (i.e there will be no needles involved).*** At your appointment for the MR scan, an investigator will go through the Screening Form with you, give you information about the study and show you the MRI system (see the picture).



You should make sure that all your questions are answered and you and your parent/guardian agree to participate in the study before signing the consent form. Before you enter the magnet room, we will ask you to remove all metal objects, such as keys, coins, since they could be attracted to the MRI scanner with great force. If a metal object hit anyone in the way, it could cause serious injury. You will be asked to change into clothing which does not contain metal. You have a choice of wearing your own clothing, if it is metal-free (e.g., jogging suit) or the hospital gowns that we can provide.
For the first scan, you will be positioned comfortably on your back for the scan of your lower leg and for the second scan you will be positioned on your stomach for a scan of your liver. You will be provided with soft earplugs to reduce the noise from the MRI scanner (the sound it produces is a loud knocking noise). For the scan of your lower leg, a special receiver will be placed just below your knee and padded to ensure that your leg does not move while we image it. You will then be slid into the large, tunnel-shaped scanner until your leg or stomach is at the centre of

the magnet. The scanner at the Health Sciences Centre has a field-strength of 1.5T (similar to most hospital MRI scanners). The tunnel is 60 cm (about 2 feet) across and is open at both ends. During the scan, the MR operator will talk with you regularly through a two-way intercom to let you know what to do. At times you will be asked to remain very still so that the images will be sharp. After the scan has been completed and you have left the magnet room, we will ask you to fill out a questionnaire about how the study went for you.

Participation in the study will be for one week but may involve a 6-month physical activity intervention if you qualify and agree to participate.

The researcher may decide to take you off this study if the funding for the study is stopped, if there is a problem with the MRI machine and we are no longer able to get images. *You can stop participation in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study staff first.*

Risks and Discomforts

Blood samples: Some people experience slight discomfort, bleeding and/or bruising during collection of blood samples. Sometimes people feel dizzy or even faint occasionally. A bruise and some swelling in your arm can develop if the testing site is not kept clean. Medical personnel will insert a catheter (needle and tube) into the forearm vein one time and the plastic tube will remain in your arm for the remaining blood samples (total 6-8 tablespoons). Every effort will be made to reduce these risks. We will have trained nurses who work with children everyday and are very comfortable with inserting needles.

Arterial Stiffness: Arterial stiffness is measured with a device called a "tonometer". This is a small piece of metal at the end of a device shaped like a pencil. A researcher will place the metal against your skin on the top of a blood vessel. We will make measurements on a vessel in your wrist and a vessel in your neck. There are no risks associated with this procedure.

Cardiopulmonary Exercise Testing: There exists the possibility of certain changes occurring during the exercise test. Serious complications of exercise testing occur in approximately 1 in 10,000 tests in adults. These may include abnormal blood pressure, fainting, disorders of heart rate and, in rare instances heart attack, stroke and death. Exercise may also cause slight injury to muscles and joints that will go away within three days

after the test. Every effort will be made to minimize these risks by reviewing information about your health and fitness before the test and by closely monitoring how your body responds to the exercise. We will reduce these risks by closely monitoring your condition throughout the exercise test and if you experience an abnormal response, the test will be stopped. Emergency equipment and trained personnel are available to deal with any situations that may arise.

Dual Energy X-ray Absorptiometry (DEXA): The physical risks associated with the scan of your whole body are considered to be low. The device uses an x-ray source to measure bone density. However, the amount of radiation is much less than a regular chest x-ray and equivalent to the radiation accumulated during one normal day.

Magnetic resonance imaging and spectroscopy: You may experience some discomfort as you will be asked to remain relatively motionless for periods of up to 45 minutes. It is not always possible to predict whether you will have these problems or not. You may also experience nervousness from confinement in a tight space (claustrophobia) and if you do become anxious, you can stop the procedure at any time using a panic button. It will help that your head will remain outside the scanner during muscle imaging and face down on a pillow during liver imaging. There are no known side effects from exposure to magnetic fields but if your have any metal clips or plates or any devices listed below in your body, you should tell the investigator about it as you will not be eligible to take part in our study. Also, MRI may not be appropriate if you have used permanent eyeliner or if you are pregnant.

List of implanted body devices and metallic parts inappropriate for magnetic resonance experiments:-

- Heart pacemaker,
- Heart valve replacement,
- Aortic clips,
- Metal fragments in body
- Brain clips or pieces of metal used in brain surgery
- Pieces of metal in the body resulting from work as a sheet-metal worker or welder
- Clips placed in an internal organ
- Prosthetic devices, such as middle ear, eye, joint, or penile implants
- Joint replacement.
- Hearing aid that cannot be removed
- Insulin pump

• Intrauterine device (IUD)
• Shunts or stents
• Metal mesh or coil implants
• Metal plate, pin, screws, or wires, or any other metal implants.

RISKS TO AN EMBRYO, FETUS, OR BREAST-FED INFANT: A female who is pregnant or is breast-feeding an infant should not participate in this research. It is not known whether MRI&S may harm an embryo or fetus or an infant who is breast-feeding. It is also not known whether MRI&S may lead to birth defects.

Pregnancy test: A pregnancy test will be performed for any female who is able to have children and wishes to participate in this research. A study doctor will ask for the date when a female's last monthly period started.

Pregnancy during participation in this research: If you are able to have children, and you suspect pregnancy during this research, you must tell your study doctor immediately. If pregnant your participation in the research will stop.

Unforeseen Risks

A previously unknown side effect may occur. It is not possible to estimate the chances of such occurrences or their severity.

How you can help reduce risks:

During your participation in this study, research personnel will watch closely to determine whether there are complications that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep appointments.
- Follow the doctors' recommendations.
- Contact us if your telephone number changes.
- Tell the research personnel if any other medical condition develops or if you begin new medication.
- Inform your parent/guardian and have them tell your regular doctor about your participation in this study.
- Talk to a family member or a friend about your participation in this research.
- Carry information about the research in your purse or wallet.

What to do if you have any problems: If you have any problems, such as unusual symptoms or pain, at any time during your participation in the

research, your study doctor can recommend treatment. Please report the problem to your study doctor promptly. Telephone numbers where he/she may be reached are listed on the first page of this consent form.

POSSIBLE BENEFITS

Benefit to you: Your study doctor cannot guarantee that you will directly benefit from participation in this research. You will receive information about your risk for diabetes that would not routinely be measured during a regular visit to the doctor. You will also receive information regarding your fitness and recommendations regarding physical activity if you are interested. You will also receive your test results so that you can give them to your primary care physician**.**

Benefit to other people with obesity or type 2 diabetes: There are a growing number of children who are considered overweight. They have an increased risk for type 2 diabetes and doctors need more information regarding risk factors that will help them prevent the disease. The information gathered in this study will help provide information regarding new risk factors that could be used to identify children who may be at an increased risk for progressing to type 2 diabetes. The findings may help reduce the number of children diagnosed with diabetes in Canada.

Costs

All the procedures, which will be performed as part of this study, are provided at no cost to you. None of the study doctors the University of Manitoba or the Manitoba Institute of Child health are receiving professional fees or personal financial support to conduct this study.

Payment for participation

You will be given $25.00 per completed study visit to a maximum of $50.00 upon termination of your participation in this research study to cover costs associated with participating such as parking fees. You will receive payment upon completion of the entire study. If you decide not to participate in the study after visit #1 we will process the payment for Visit #1 after confirming with you would like to withdraw from the study.

Confidentiality

Information gathered in this research study may be published or presented in public forums, however your name and other identifying information will not be used or revealed. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. All study documents will refer to you with a number and your initials to protect your privacy.

Normally, only people directly involved with the research procedure are allowed in the study area. If the study takes place at the Health Sciences Center which is a clinical facility, people not involved in the research study may occasionally require access. All staff at the Health Sciences Centre are required to keep health information confidential, in accordance with the Health Information Act of Manitoba.

All data obtained during your MRI scan will be stored with an alpha-numerical code instead of your name. Only your file, which is kept in Dr. McGavock's office in a locked filing cabinet, will have information which relates your name to the code. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Organizations that may inspect and / or copy your research results for quality assurance and data analysis include groups such as the National Research Council Research Ethics Board and The University of Manitoba Health/Biomedical Research Ethics Board,

Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. The study doctor's will need to have access to your medical records to keep track of any events that may occur during the study. This is a very common practice at the University and is done for the protection of children participating in research.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:
We applied to various agencies, including the SickKids Foundation and the Canadian Diabetes Association to help fund this research. These agencies may request access to the information we collect during the course of this investigation.

The University of Manitoba Biomedical Research Ethics Board may review records related to the study for quality assurance purposes.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary and also depends upon your willingness to provide informed consent to participate. Your parent/guardian may refuse to let you participate or you may withdraw you from the study at any time. Your decision not to participate or to withdraw from the study will not affect the care you will receive at this centre. If the study staff feels that it is in your best interest to withdraw from the study, they will do so without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Medical Care for Injury Related to the Study

In the case of injury or illness resulting from this study, necessary medical treatment will be available at no additional cost to you.

What else should I know?

Although the MRI for this study is not a diagnostic scan and any images obtained are for research purposes only, it is possible that the MR scan may disclose an unknown abnormality. Should this occur, you have a choice of whether you would like your doctor to be informed or not. The sooner your doctor knows, the earlier a proper follow-up may begin. If you choose to have your physician informed, a medical imaging specialist will review the images and we would send a report to your physician. On the other hand, because this research is not a diagnostic examination, you may prefer not to have any problems investigated. You have every right not to let your doctor know should an abnormality be detected in your scan.

In summary, if we observe a possible abnormality during our routine processing of the research images and you have indicated on the enclosed consent form that you wish your doctor to be informed, we will then have a medical imaging specialist review the images. If the specialist agrees that further follow-up is advisable, we will contact your doctor, who in turn will contact you for follow-up with the necessary proper diagnostic tests. If you have indicated that you don't want your doctor to be informed, we will have the image reviewed by a medical imaging specialist and neither you nor your doctor will be contacted regarding a possible abnormality.

Please contact us if you would like any more information about the study. Please let us know if you would like copies of any published scientific reports about the research project.

Questions

You are free to ask any questions that you may have about this investigation and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact the study doctor and the study staff:

Name	Phone	Pager
Jonathan McGavock, PhD	480-1359	
Heather Dean, MD	787-7435	
Elizabeth Sellers, MD	787-7435	
Lawrence Ryner, PhD	984-7693	
Phillip Gardiner, PhD	474-7087	

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at (204) 789-3389

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

In case of a possible abnormality showing up on the MR scan,
☐ I wish my doctor, Dr. _____, be informed.
☐ I do not wish my doctor be informed.

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Dr. Jonathan McGavock and or his/her study staff. I have had my questions answered by them in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship (such as employer, supervisor or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my health records that relate to this study by The University of Manitoba Research Ethics Board, for quality assurance purposes.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

I agree to be contacted for future follow-up in relation to this study,
Yes _ No _

Participant signature_____
Date _____

Participant printed name: _____

Parent/legal guardian's signature _____
Date _____

(day/month/year)
Parent/legal guardian's printed name: _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Printed Name: _____Date _____

(day/month/year)

Signature: _____

"Role in the study: _____

Relationship (if any) to study team members:_____

Appendix 4: Consent form Study C

Study Date:_____

Participant #: _____

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: "Cardiorespiratory fitness, steatosis and insulin resistance in adolescents at risk for and diagnosed with type 2 diabetes"
- Physical Activity Intervention.

PROTOCOL #: **B2006:091**

SPONSOR: **Manitoba Children's Hospital Foundation**

INVESTIGATORS:

Jonathan McGavock, PhD	Pediatrics	480-1359
Dean Kriellaars, PhD	Rehab. Medicine	787-3505
Heather Dean, MD	Pediatrics	787-7435
Elizabeth Sellers, MD	Pediatrics	787-7435
Lawrence Ryner, PhD	Radiology	984-7693
Phillip Gardiner, PhD	Physiology	474-7087

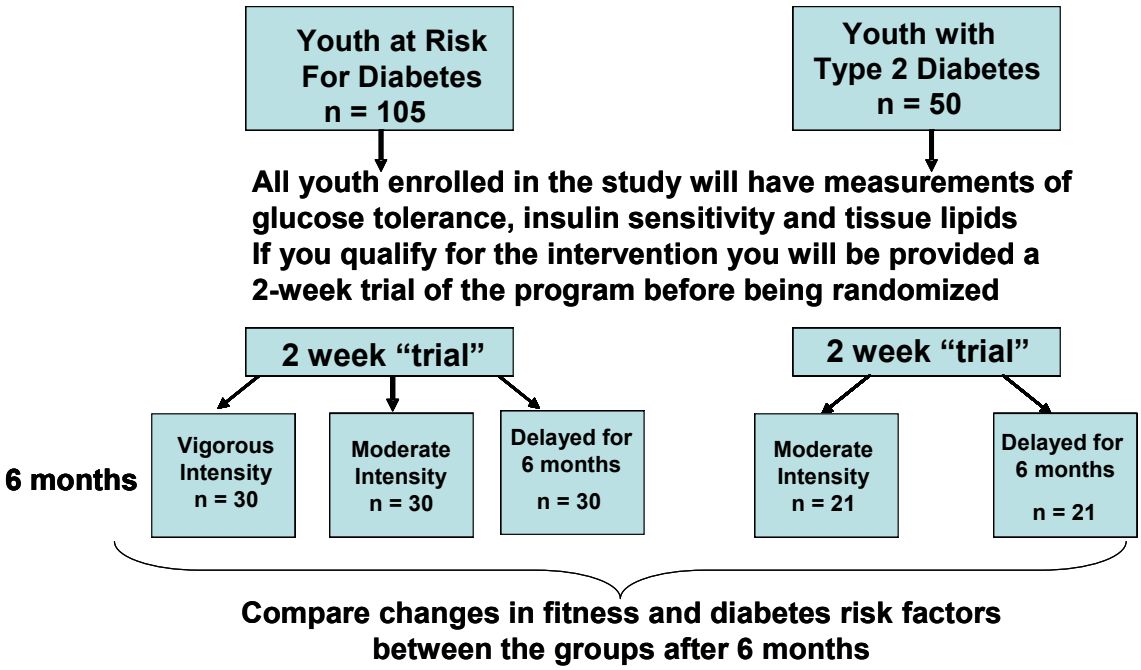
You are being asked to participate in a research study involving several visits to determine if increased physical activity changes certain risk factors for type 2 diabetes. Before you agree to participate we will also require that your parent or guardian consent to your participation. Please take your time to review this consent form with your parent or guardian and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your parents, friends, family or your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Purpose of Study

Physical activity is an important lifestyle factor in the treatment and prevention of type 2 diabetes. Studies in adults show that increased activity reduces the risk for diabetes and improves the body's ability to manage blood sugar. Little information is available describing the dose of exercise on diabetes risk or blood

sugar control in adolescents. If you agree to participate in this study we will do two tests for diabetes risk, a test of exercise ability and an MRI of your muscle and liver before and after a 6-month physical activity intervention. MRI is a large magnet that we use to take pictures of muscles and organs inside your body. It is not harmful to you and will not require any needles. The MRI of the muscle is a new method to measure fat inside muscle and the liver without using a needle and may provide information about your risk for diabetes.

Am I Eligible to Participate? We plan to study approximately 50 youth with type 2 diabetes and 90 youth without diabetes but who are considered at risk for type 2 diabetes. After the preliminary measurements, all youth will be randomly assigned to one of three physical activity intervention groups: (1) Delayed start (control); (2) vigorous intensity or (3) moderate intensity.



The study is purely voluntary and if you decide not to participate or withdraw, your normal medical care will not be affected in any way.

For all groups, all subjects who participate in this research study must be between 13 and 18 yrs of age and must pass a medical screen by his/her physician. If any of the following applies to you, you may not participate in the study:

6. You have metal objects inside your body. MRI may be dangerous for anyone with metal implants or metal objects inside their body.
7. You, in the opinion of the screening physician or investigators, have a medical condition that could be made worse by any stress associated with participation in a research protocol. These conditions include heart and circulatory problems, seizure disorders, anxiety disorders, and mental disorders.
8. You are unable to exercise on a daily basis.
9. You have claustrophobia.
10. You are or may be pregnant.
11. You weigh more than 350 pounds.

Study procedures

Schedule of Study Visits

Visit	Purpose	Duration	Location
#1	Baseline Assessment of Diabetes risk (OGTT) Exercise Tolerance, and muscle mass (DEXA).	3 hours (week day)	Manitoba Institute of Child Health 5th Floor John Buhler Research Center 715 McDermott Ave. Phone: 480-1359 or 789-3591
#2	Arterial stiffness and Insulin sensitivity	4 hours	
#3	MRI imaging of muscle and liver	1 hour (Friday)	
	Physical activity intervention started immediately or delayed for six months.	3 one-hour visits/week for a period of 6 months	
#4	Follow-up assessment of exercise tolerance, and muscle mass.	3 hours (week day)	
#5	Arterial stiffness and Insulin sensitivity	4 hours	
#6	Follow-up MRI imaging of muscle and liver	1 hour (Friday)	

The primary goal of this study is to see if physical activity changes the levels of fat inside the muscles and liver of youth at risk for or diagnosed with type 2 diabetes. We will also measure insulin sensitivity, which is a term we use to describe how well your body handles sugar after a meal and it gives us information about your risk for diabetes. We can test insulin sensitivity using a glucose test described below. If you agree to participate you will be placed into one of three groups: (1) vigorous physical activity; (2) moderate intensity physical activity or (2) delayed Physical activity of your choice after 6 months of regular activities of daily living (control). The choice of study group is not up to you or your study doctor, but will be determined by chance (i.e. drawing straws). Regardless of when you start, you will receive a structured, supervised exercise program tailored to your needs.

What will I have to do if I participate?

Visit #1 – Exercise test / Diabetes Screening visit.

You will arrive at the John Buhler Research Centre at 8:00am. You cannot eat anything before arriving to the University and we ask that you not eat any food after 10 pm the night before. Someone will meet you at the front doors of the centre and escort you up to the lab. We will explain the study in detail and ask any questions you may have. After you and your parent/guardian have signed the consent form a nurse will insert a catheter (a needle and plastic tube) into a vein in your arm. You will have the option of using a special cream (called EMLA) used to numb the area where we will insert the needle. A small plastic tube will remain in your arm and be used to sample blood in small amounts during the test. We will use these samples to measure blood sugar levels, cholesterol, insulin, and the activity of energy producing cells (known as mitochondria) work in your system. After collecting a few samples you will consume a sugar drink. After finishing the drink, we will collect blood samples at 15, 30, 60, 90 and 120 minutes, from the tube that will remain in your arm. After the test we will provide you with a light lunch then escort you to the exercise lab, where you will change into clothes appropriate for exercising.

Once changed, we will escort you to a quiet room where we will perform a scan of your body that measures the amount of muscle, fat and bone inside your body. This test takes approximately 10 minutes to perform and all you have to do is lie still while a scan moves across your body. The machine takes an x-ray (picture) of your body that we can use to measure the size of your muscles. The amount of x-ray used in this test amounts to less than a regular chest x-ray and is similar to the amount of radiation a person is exposed to in the environment on a daily basis. Some

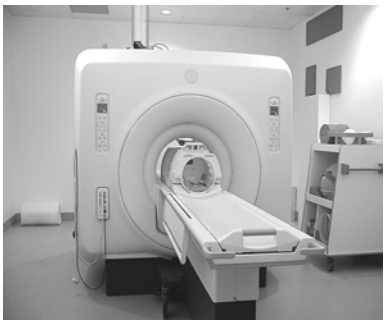
researchers equate this to one commercial flight across Canada or living for one day in the city. **This test is completely safe and no needles are involved.**

The exercise test will be performed on a stationary bicycle. We will measure your heart rate and blood pressure throughout the test. Heart rate is measured with a small black band around your chest and blood pressure is measured with a cuff on your arm. We will also measure the air you exhale (breath out) during the exercise. After you start pedaling, we will increase the resistance on the pedals every two minutes. As the exercise becomes more difficult we will encourage you to continue until you are no longer able to pedal. When you can no longer keep pedaling we will stop the exercise test. You will be the one who decides when to stop exercising, the study doctors will only encourage you to continue as long as you can. The amount of oxygen in your breath at the end of the test will give us an estimate of your current fitness level. After completing the exercise test we will monitor you for a period of 20 minutes and you will be free to go.

Visit #2 - You will arrive at the John Buhler Research Centre between 7 and 7:30 am. You cannot eat anything before arriving to the University and we ask that you not eat any food after 10 pm the night before. We will escort you up the Institute for Child Health on the 5th floor where we will explain the study in detail and answer any questions you may have. A trained nurse will insert a catheter into a vein in your arm and another into your hand. One small tube will be used for collecting blood and the other will be used to inject a small amount of sugar into your body. We will start by taking three blood samples (-15 , -10 and -2 min) before injecting the sugar and at 8:00 am we will inject a sugar solution into one of the small tubes. The amount of sugar is very small and contains the same number of calories that are in an apple. This test will provide information about how the various systems in your body react to sugar, which will help us understand your risk for diabetes. After injecting glucose we will take small blood samples at 2,3,4,5,6,8,10,14 and 19 min than we will inject a very small amount of insulin to help return your blood sugar to normal levels (the amount injected will be a small fraction of the amount of insulin a child with diabetes would inject to control their blood sugar). After the injection of insulin we will take blood samples at 22,25,26,30,40,50,70,100, 140 and 180 min. The amount of blood removed for each sample is no bigger than a teaspoon and total amount of blood we take will be less than half of the size of a small (250 mL) juice box.

During the blood sampling one of the research assistants will make repeated measurements of the pressure in a blood vessel in your wrist

and your neck. This test does not involve a needle. Instead we will place a small metal device the size of a pen against your skin. This device will estimate the pressure in your blood vessel and provide us with information about the stiffness of your blood vessels. You will not experience any pain or discomfort during the measurements. We will make the measurements every 15 minutes during the test. After this test we will provide a light breakfast. After this test we will provide a light breakfast and you will change into clothes appropriate for an exercise test.



Visit #3 – Will likely take place on a Friday as this is the only time we will have access to the MRI machine at the Health Sciences Centre. You do not have to fast overnight for this visit, but we ask that you arrive to the lab between 2:45 and 3:45pm in the afternoon. A member of our staff will meet you are the front door of the John Buhler Research Centre (735 McDermot ave.). The MRI will take approximately 1 hour and all you have to do is lie still and listen to music. ***This test is completely non-invasive (i.e. there will be no needles involved).*** At your appointment for the MR scan, an investigator will go through the Screening Form with you, give you information about the study and show you the MRI system (see the picture).

You should make sure that all your questions are answered and you and your parent/guardian agree to participate in the study before signing the consent form. Before you enter the magnet room, we will ask you to remove all metal objects, such as keys, coins, since they could be attracted to the MRI scanner with great force. If a metal object hit anyone in the way, it could cause serious injury. You will be asked to change into clothing which does not contain metal. You have a choice of wearing your own clothing, if it is metal-free (e.g., jogging suit) or the hospital gowns that we can provide.

For the first scan, you will be positioned comfortably on your back for the scan of your lower leg and for the second scan you will be positioned on your stomach for a scan of your liver. You will be provided with soft earplugs to reduce the noise from the MRI scanner (the sound it produces is a loud knocking noise). For the scan of your lower leg, a special receiver will be placed just below your knee and padded to ensure that your leg does not move while we image it. You will then be slid into the large, tunnel-shaped scanner until your leg or stomach is at the centre of the magnet. The scanner at the Health Sciences Centre has a field-

strength of 1.5T (similar to most hospital MRI scanners). The tunnel is 60 cm (about 2 feet) across and is open at both ends. During the scan, the MR operator will talk with you regularly through a two-way intercom to let you know what to do. At times you will be asked to remain very still so that the images will be sharp. After the scan has been completed and you have left the magnet room, we will ask you to fill out a questionnaire about how the study went for you.

These two visits will be repeated at the end of a six month intervention period to determine if there were any changes in these variables during that time frame.

Physical Activity Intervention – After the first two visits all youth will receive two weeks of structured physical activity provided by the study doctors. Members of the study team will supervise exercise visits on treadmills and stationary bicycles located at one of the three YMCA facilities three days per week. You are required to attend a minimum of four visits over the course of this "run-in" phase to be considered eligible for the study. After the two week phase you will be placed into one of three groups: (1) vigorous intensity; (2) moderate intensity or (3) delayed start (control). The choice of when you start is "random", meaning that we have a computer decide and neither you or your doctor can influence the decision. The order is determined by a statistician at the University of Manitoba to ensure fairness to all participants. Children in the vigorous or moderate intensity groups will begin exercise immediately, while those in the delayed phase will begin exercise six months after the run-in phase (they will be considered as "controls"). Regardless of the phase of the study you enter, you will be asked to return for follow-up measurements described above six months after the initial visit.

The physical activity intervention is a 3-5-day/week program that involves walking on a treadmill (or outside if weather permits) and cycling on a stationary bicycle. Three days of the week, you will come to one of the four YMCA locations in Winnipeg to perform the exercise under the supervision of a trained professional. The other two days of the week we ask that you walk in your neighbourhood or at a nearby park for 30-60 minutes. We will provide you with a heart rate monitor to wear to record each of the home-based activity sessions. The daily exercise sessions will initially last 30 minutes and progressively increase to 60 minutes. The intensity will also increase gradually over the six-month period. For youth in the vigorous intensity group, they will perform 30 minutes of activity with brief increases in the speed or hill on the treadmill which will increase your heart rate. The youth in the moderate intensity group will not get their

heart rate up as high but will exercise a little longer to burn the same number of calories. Adolescents in the delayed-intervention group will receive six months of supervised exercise training at the YMCA which will be supervised by the research team and you will get to choose the regime you want. Follow-up measurements of your risk for diabetes will be available at six months after starting the training regime to determine the effectiveness of the activity on your risk for type 2 diabetes.

Participation in the study will be for a period of approximately 7 months.

The researcher may decide to take you off this study if the funding for the study is stopped, if there is a change in your medical condition that would prevent you from exercising or requiring you to receive additional therapy that would exclude you from the study. You *can withdraw from the study at any time. However, if you decide to stop participating, we encourage you to talk to the study staff first.*

Risks and Discomforts

Blood samples: Some people experience slight discomfort, bleeding and/or bruising during collection of blood samples. Sometimes people feel dizzy or even faint occasionally. An infection in your arm can develop if the testing site is not kept clean. Medical personnel will insert a catheter (needle and tube) into the forearm vein one time and the plastic tube will remain in your arm for the remaining blood samples (total 6-8 tablespoons). Every effort will be made to reduce these risks. We will have trained nurses who work with children everyday and are very comfortable with inserting needles.

Arterial Stiffness: Arterial stiffness is measured with a device called a "tonometer". This is a small piece of metal at the end of a device shaped like a pencil. A researcher will place the metal against your skin on the top of a blood vessel. We will make measurements on a vessel in your wrist and a vessel in your neck. There are no risks associated with this procedure.

Cardiopulmonary Exercise Testing and Training: There exists the possibility of certain changes occurring during the exercise test. Serious complications of exercise testing occur in approximately 1 in 10,000 tests in adults. These may include abnormal blood pressure, fainting, disorders

of heart rate and, in rare instances heart attack, stroke and death. Exercise may also cause slight injury to muscles and joints that will go away within three days after the test. Every effort will be made to minimize these risks by reviewing information about your health and fitness before the test and by closely monitoring how your body responds to the exercise. We will reduce these risks by closely monitoring your condition throughout the exercise test and training. If you experience an abnormal response, to exercise, the session will be stopped. Emergency equipment and trained personnel are available to deal with any situations that may arise.

Dual Energy X-ray Absorptiometry (DEXA): The physical risks associated with the scan of your whole body are considered to be low. The device uses an x-ray source to measure bone density. However, the amount of radiation is much less than a regular chest x-ray and equivalent to the radiation accumulated during one normal day.

Potential Risks to your Insurance: There is a possibility that a diagnosis of type 2 diabetes, high cholesterol or blood pressure may have a negative impact on the cost of medical insurance for you in the future. This risk would be the same if you were diagnosed at your doctors office or within a hospital setting.

Magnetic resonance imaging and spectroscopy: You may experience some discomfort as you will be asked to remain relatively motionless for periods of up to 45 minutes. It is not always possible to predict whether you will have these problems or not. You may experience nervousness from confinement in a tight space (claustrophobia) and if you do become anxious, you can stop the procedure at any time using a panic button. It will help that your head will remain outside the scanner during muscle imaging and face down on a pillow during liver imaging. There are no known side effects from exposure to magnetic fields but if you have any metal clips or plates or any devices listed below in your body, you should tell the investigator about it as you will not be eligible to take part in this phase of the study. Also, MRI may not be appropriate if you have permanent eyeliner or eyebrows or if you are pregnant.

List of implanted body devices and metallic parts inappropriate for magnetic resonance experiments:-

- Heart pacemaker,
- Heart valve replacement,
- Aortic clips,

• Metal fragments in body
• Brain clips or pieces of metal used in brain surgery
• Pieces of metal in the body resulting from work as a sheet-metal worker or welder
• Clips placed in an internal organ
• Prosthetic devices, such as middle ear, eye, joint, or penile implants
• Joint replacement.
• Hearing aid that cannot be removed
• Insulin pump
• Intrauterine device (IUD)
• Shunts or stents
• Metal mesh or coil implants
• Metal plate, pin, screws, or wires, or any other metal implants.

RISKS TO AN EMBRYO, FETUS, OR BREAST-FED INFANT: A female who is pregnant or is breast-feeding an infant should not participate in this research. It is not known whether MRI&S may harm an embryo or fetus or an infant who is breast-feeding. It is also not known whether MRI&S may lead to birth defects.

Pregnancy test: A pregnancy test will be performed for any female who is able to have children and wishes to participate in this research. A pregnancy test may be repeated later. A study doctor will ask for the date when a female's last monthly period started.

Pregnancy during participation in this research: If you are able to have children, and you suspect pregnancy during this research, you must tell your study doctor immediately. Your participation in the research will stop if you become pregnant.

Unforeseen Risks

A previously unknown side effect may occur. It is not possible to estimate the chances of such occurrences or their severity.

How you can help reduce risks:

During your participation in this study, research personnel will watch closely to determine whether there are complications that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep appointments.
- Follow the doctors' recommendations.
- Contact us if your telephone number changes.
- Tell the research personnel if any other medical condition develops or if you begin new medication.

- Have your parent or guardian inform your regular doctor about your participation in this study.
- Talk to a family member or a friend about your participation in this research.
- Carry information about the research in your purse or wallet.

What to do if you have any problems: If you have any problems, such as unusual symptoms or pain, at any time during your participation in the research, your study doctor can recommend treatment. Please report the problem to your study doctor promptly. Telephone numbers where he/she may be reached are listed on the first page of this consent form.

POSSIBLE BENEFITS

Benefit to you: Your study doctor cannot guarantee that you will directly benefit from participation in this research. You will receive information about your risk for diabetes that would not routinely be measured during a regular visit to the doctor. You will also receive information regarding your fitness and recommendations regarding physical activity if you are interested. The physical activity intervention will be provided at no cost to you and may help lower your risk for type 2 diabetes. You will be provided with access to an exercise facility and learn important life skills regarding the benefits of daily physical activity. You will also receive your test results so that your parent/guardian can give them to your primary care physician**.**

Benefit to youth who are at risk for or currently have type 2 diabetes: There are a growing number of youth who are considered at risk for type 2 diabetes and doctors need more information regarding risk factors that will help them prevent the disease. The information gathered in this study will help provide information regarding new risk factors that could be used to identify youth who may be at an increased risk for progressing to type 2 diabetes. The information gathered here will provide physicians with important information regarding the benefit of physical activity in the treatment and prevention of type 2 diabetes. The findings may help reduce the number of youth diagnosed with diabetes in Canada.

Costs All the procedures, which will be performed as part of this study, are provided at no cost to you or your parent/guardian. None of the study doctors, the University or the Manitoba Institute of Child health are receiving professional fees or personal financial support to conduct this study.

Payment for participation

You will be given $25.00 per completed testing visit to a maximum of $150.00 upon termination of your participation in this research study to cover costs associated with participating such as parking fees. You will not be compensated for the physical activity intervention visits. You will receive payment upon completion of the entire study. If you decide not to participate in the study after visit #1 we will process the payment for Visit #1 after confirming with you and your parent/guardian that you would like to withdraw from the investigation.

Confidentiality

Information gathered in this research study may be published or presented in public forums, however your name and other identifying information will not be used or revealed. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. All study documents will refer to you with a number and your initials to protect your privacy

Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. The study doctors will need to have access to your medical records to keep track of any events that may occur during the study. This is a very common practice at the University and is done for the protection of youth participating in research.

Normally, only people directly involved with the research procedure are allowed in the study area. Because the study takes place at the Health Sciences Center which is a clinical facility, people not involved in the research study may occasionally require access. All staff at the Health Sciences Centre are required to keep health information confidential, in accordance with the Health Information Act of Manitoba.

All data obtained during your MRI scan will be stored with an alpha-numerical code instead of your name. Only your file, which is kept in Dr. McGavock's office in a locked filing cabinet, will have information which relates your name to the code. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as: Organizations that may inspect and / or copy your research results for

quality assurance and data analysis, including; the SickKids Foundation and the Canadian Diabetes Association who may help fund the study. In addition, the National Research Council Research Ethics Board and The University of Manitoba Health/Biomedical Research Ethics Board have the right to inspect / copy the data collected.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary and also depends upon your willingness to provide informed assent to participate. You may refuse to participate or you may withdraw from the study at any time. Your decision not to participate will not affect your care at this centre. If the study staff feel that it is in your best interest to withdraw from the study, we will remove you from the study without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Medical Care for Injury Related to the Study

In the case of injury or illness resulting from this study, necessary medical treatment will be available at no additional cost to you.

What else should I know?

Although the MRI for this study is not a diagnostic scan and any images obtained are for research purposes only, it is possible that the MR scan may disclose an unknown abnormality. Should this occur, you have a choice of whether you would like your doctor to be informed or not. The sooner your doctor knows, the earlier a proper follow-up may begin. If you choose to have your physician informed, a medical imaging specialist will review the images and we would send a report to your physician. On the other hand, because this research is not a diagnostic examination, you may prefer not to have any problems investigated. You have every right not to let your doctor know should an abnormality be detected in your scan.

In summary, if we observe a possible abnormality during our routine processing of the research images and you have indicated on the enclosed consent form that you wish your doctor to be informed, we will then have a medical imaging specialist review the images. If the specialist agrees that further follow-up is advisable, we will contact your doctor, who in turn will contact you for follow-up with the necessary proper diagnostic tests. If you have indicated that you don't want your doctor to be informed, we will not have the image reviewed by a medical imaging

specialist and neither you nor your doctor will be contacted regarding a possible abnormality.

Please contact us if you would like any more information about the study. Please let us know if you would like copies of any published scientific reports about the research project.

Questions

You are free to ask any questions that you may have about this investigation and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact the study doctor and the study staff:

Name	**Phone**
Jonathan McGavock, PhD	480-1359
Heather Dean, MD	787-7435
Elizabeth Sellers, MD	787-7435
Dean Kriellaars, PhD	787-3505
Phillip Gardiner, PhD	474-7087
Lawrence Ryner, PhD	984-7693

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at (204) 789-3389

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

In case of a possible abnormality showing up on the MR scan,
☐ I wish my doctor, Dr. _____, be informed.
☐ I do not wish my doctor be informed.

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Dr. Jonathan McGavock and or his/her study staff. I have had my questions answered by them in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship (such as employer, supervisor or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my health records that relate to this study by The University of Manitoba Research Ethics Board, for quality assurance purposes.

By signing this consent form, I have not waived any of my legal rights as a participant in a research study.

I agree to be contacted for future follow-up in relation to this study,
Yes _ No _

Participant signature_____

Date _____

Participant printed name: _____

Parent/legal guardian's signature_____

Date _____

(day/month/year)

Parent/legal guardian's printed name: _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Printed Name: _____

Date _____

Signature: _____

"Role in the study: _____

Relationship (if any) to study team members:_____

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