

**Frequency and intensity of physical activity are associated with insulin resistance in First Nations children and adolescents in 2 remote villages in northern British Columbia, Canada**

By

Marc Mitchell  
B.Sc., B.PHE. Queen's University, 2004

A thesis submitted in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

In the School of Exercise Science, Physical and Health Education,  
University of Victoria

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### ABSTRACT

**Objective:** To explore the association of insulin resistance (IR) with direct measures of physical activity (PA).

**Research methods and procedures:** A school-based, cross-sectional study was conducted in two remote British Columbia coastal First Nations villages. 74 healthy boys and girls (mean = 11.8yrs  $\pm$  2.2; range = 8.8-18.5yrs) volunteered to participate. PA was measured with the ActiGraph accelerometer. IR was determined using the homeostasis model assessment of insulin resistance (HOMA-IR). Body mass index standardized for age and sex (zBMI) and waist circumference were used to assess total and central adiposity.

**Results:** From the 39 participants with complete data sets, moderate to vigorous intensity physical activity (MVPA) was inversely related to HOMA-IR ( $r = -.45$ ,  $p < 0.01$ ) while total and central adiposity were directly related ( $r = .44$ ,  $p < 0.01$  and  $r = .35$ ,  $p < 0.05$ , respectively).

**Discussion:** These data provide evidence of the important role of PA, particularly MVPA, in improving IR and potentially preventing type 2 diabetes in First Nations youth.

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**Abbreviations**

24-FRQ	24-Hour Food Recall Questionnaire
AS! BC	Action Schools! BC
BMI	Body Mass index
CRF	Cardio-respiratory fitness
D2	Type 2 Diabetes Mellitus
FFQ	Food Frequency Questionnaire
IR	Insulin Resistance
IS <sub>EU</sub>	Euglycemic-hyperinsulinemic clamp
MVPA	Moderate- to vigorous-intensity physical activity
OGTT	Oral Glucose Tolerance Test
PA	Physical Activity

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## **Dedications**

To my beautiful bride-to-be, my devoted parents, and my three wonderful sisters, thank you for all of your love and support.

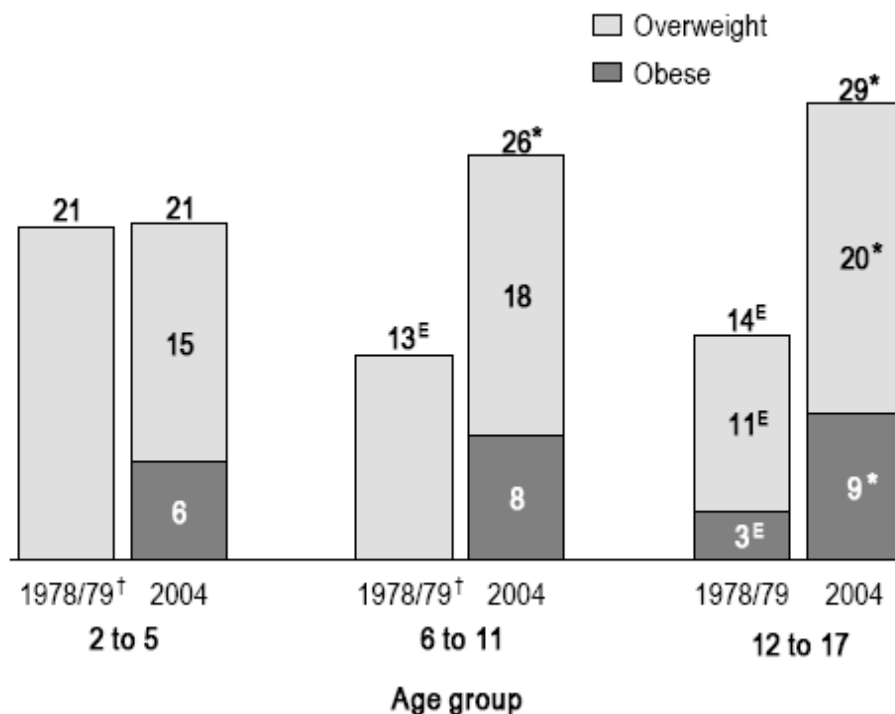
## **Chapter 1: Introduction**

### *Introduction*

Canadian youth are increasingly inactive. More than half of Canadians between the ages of 5 and 17 are not physically active enough for optimal growth and development (Public Health Agency of Canada, 2002). Similarly, just over half of First Nations youth between the ages of 12 and 17 do not accumulate sufficient physical activity (PA) on 5 or more days of the week (at least 30 minutes of moderate to vigorous activity) (First Nations Information Governance Committee, 2005). An even greater proportion of 9 to 11 year old First Nations youth, about two-thirds, are unlikely to participate in moderate to vigorous physical activity (MVPA) every day of the week (First Nations Information Governance Committee, 2005). The current low levels of PA are partly due to the fact that the physical demands of everyday life have generally decreased. This is particularly true in First Nations populations where traditional physical activities such as hunting and trapping have diminished in the face of industrialization and increased migration to urban environments (First Nations Information Governance Committee, 2005).

As levels of PA have decreased in the past two decades, the prevalence of overweight and obesity in Canadian youth has increased. This trend is consistent with literature linking physical inactivity with overweight and obesity in children (Froberg & Andersen, 2005). In 2006, the combined prevalence of overweight and obesity among children and adolescents aged 2 to 17yrs for each sex was about 70% higher than in 1978/79, and the prevalence of obesity alone was 2.5 times higher (Shields, 2006). Among youth aged 12 to 17yrs, the prevalence of overweight and

obesity has more than doubled, while the prevalence of obesity alone has tripled (Figure 1) (Shields, 2006).

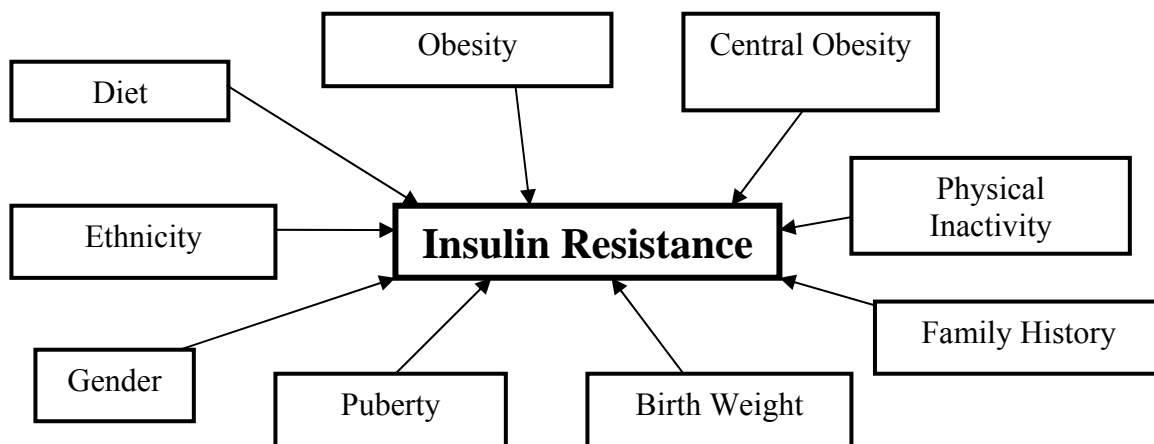


**Figure 1.** Percentage overweight and obese, by age group, household population aged 2 to 17, Canada excluding territories, 1978/79 and 2004. \*Significantly different for estimates from 1978/79; E, coefficient of variation between 16.6% and 33.3% (Interpret with caution). (From Shields, 2006)

Unfortunately, the trend has been even more extreme in First Nations children, where the proportion of obese youth under the age of 12 yrs is about 33% (First Nations Information Governance Committee, 2005), or 2.5 times the Canadian national average (Select Standing Committee on Health, 2006).

Obesity is associated with insulin resistance (IR) (Figure 2) (Krekoukia et al., 2007), a metabolic condition in which the amount of insulin secreted into the blood becomes insufficient to adequately transport glucose from the blood to muscle, fat and liver cells. With IR blood glucose levels are unmanaged and can manifest in

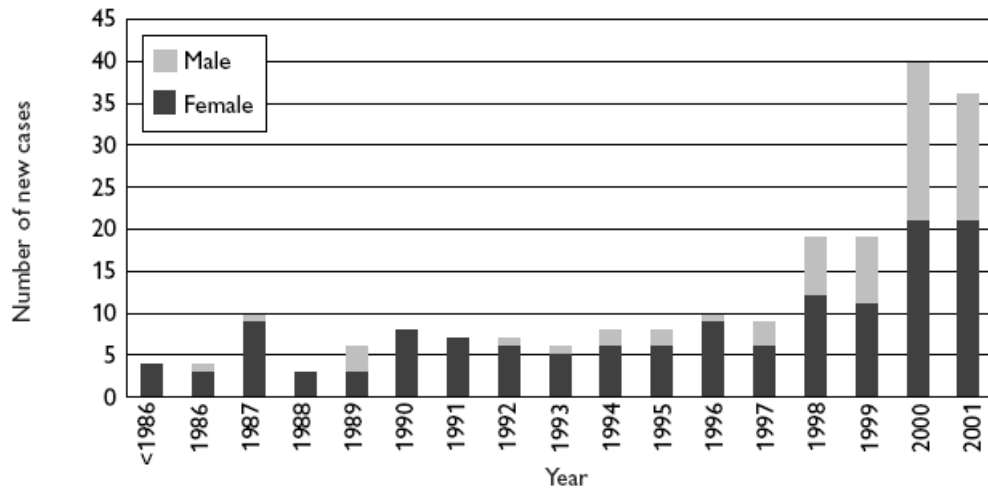
damaged insulin-producing and secreting pancreas cells. Type 2, or adult-onset, diabetes mellitus (D2) is usually the result.



**Figure 2.** Obesity and other insulin resistance risk factors.

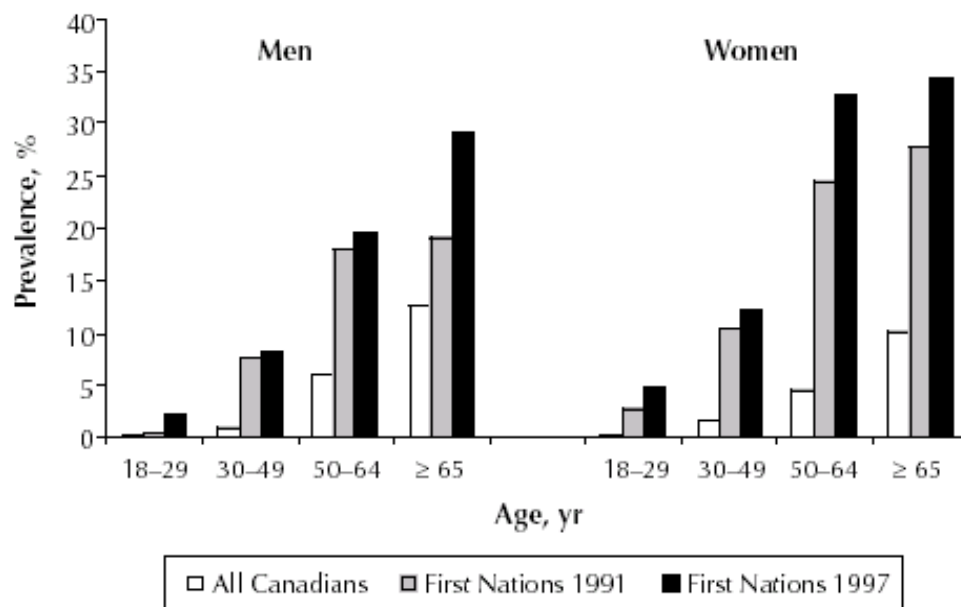
Research has consistently shown that obese youth are more insulin resistant than their lean counterparts (Krekoukia et al., 2007). While obesity is not necessary for the development of D2, it certainly advances the disease. In fact, the increase in the prevalence of D2 among children worldwide, as demonstrated in the United States, Canada, Japan, Hong Kong, Australia, New Zealand, Libya, and Bangladesh, coincides with the rising prevalence of paediatric overweight and obesity (Fagot-Campagna, 2000). This trend is also evident amongst First Nations youth, where the rapid evolution of D2 in certain parts of Canada has mirrored the increases in overweight and obesity in the past 2 decades (Dean, Sellers, & Young, 2003). As evidence of this, the number of new D2 cases, for instance, referred to the Manitoba

Diabetes Education Resource for Children and Adolescents has increased considerably in the past 20 years (Figure 3) (Dean et al., 2003).



**Figure 3.** Incidence of type 2 diabetes in youth referred to the Manitoba Diabetes Education Resource for Children and Adolescents by calendar year and gender. (From Dean et al., 2003)

Regrettably, First Nations people are 3 to 5 times more likely to develop D2 than the general Canadian population (Young, Dean, Flett, & Wood-Steiman, 2000). Figure 4 illustrates the prevalence of self-reported diabetes among all Canadians (1994) and First Nations people (1991 and 1997) (Young, Reading, Elias, & O'Neil, 2000). Given the recent D2 trend the consensus among health professionals and researchers is that First Nations people are extremely susceptible to D2.



**Figure 4.** Prevalence of self-reported diabetes among First Nations people and all Canadians. (From Young et al., 2000)

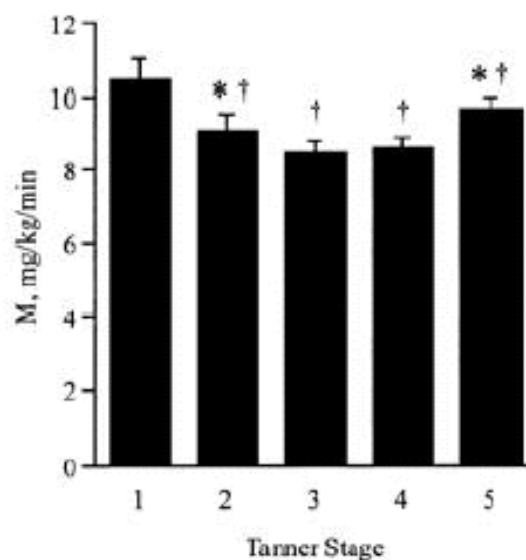
Fifty years ago D2 was virtually unknown in First Nations communities (Ministry of Health Planning, Provincial Health Officer, 2002). The disease has only recently surfaced even though First Nations genetics have not likely changed, implying that environmental factors have a strong influence on the progression of the disease. Obesity, due in large part to chronically low levels of PA, has been a major contributor to the recent D2 phenomenon in First Nations people. The apparent ethnic preference for D2 and the familial clustering of the disease suggest a strong genetic component as well (Wallerstein, 2002). This supports the concept that D2 results from a complex interaction between environmental and genetic factors (Greenspan & Gardner, 2004).

It has been determined that PA reduces IR through its effects on adiposity (Knip & Nuutinen, 1993). Several studies in adults and children have also found that PA improves IR in the absence of changes in body composition (Nassis et al., 2005;

Kahle, Zipf, Lamb, Horswill, & Ward, 1996). These findings suggest that PA has mechanisms for altering IR that are independent of adiposity. Possible mechanisms include structural and biochemical changes in skeletal muscle (Goodyear & Kahn, 1998).

Efforts to promote PA early in the lives of youth (i.e. before puberty) are crucial. As children enter puberty, they invariably go through a phase of IR due to mechanisms related to maturation. This pubertal phase is believed to play a key role in healthy somatic growth (Goran & Gower, 2001). Moran et al. (1999) determined that IR increases by approximately 25 to 30% during puberty (Figure 5).

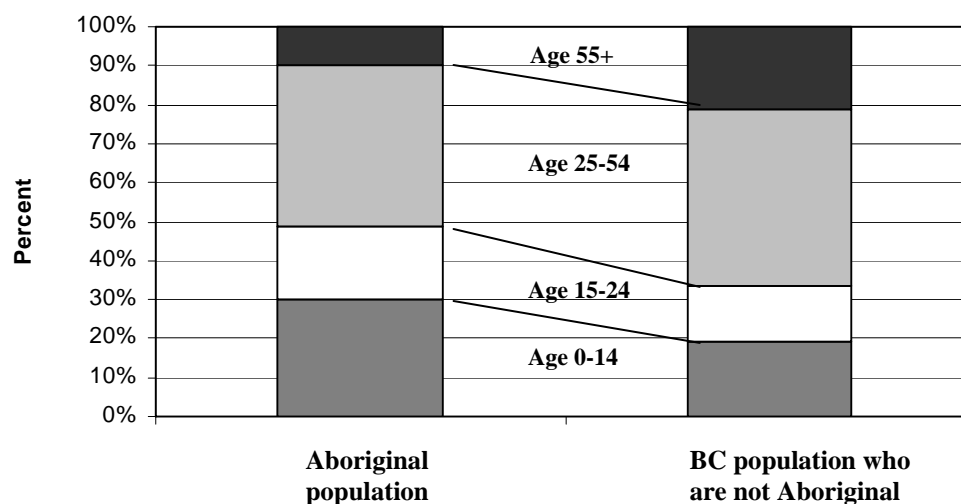
Unfortunately, in overweight and/or inactive children, pubertal IR often advances pre-diabetes to full blown D2 making the time before puberty important for the prevention of future health complications (Moran et al., 1999).



**Figure 5.** Insulin sensitivity (M) by Tanner (pubertal) stage, adjusted for sex and body mass index. A lower M value represents greater insulin resistance. Data are expressed as means  $\pm$  SE. \* $p < 0.05$  compared with preceding Tanner stage, † $p < 0.05$  compared with T1. (From Moran et al., 1999)

Cardiovascular disease (CVD) risk factors, such as physical inactivity and IR, in early childhood have also been linked to physical inactivity and IR later in life, further supporting the view that early intervention is critical for the prevention of D2 (Froberg & Andersen, 2005).

The long term health consequences of D2 are serious (i.e. kidney disease, stroke, glaucoma and retinopathies) and the life expectancy of people living with D2 may be 5 to 10 years shorter than those living without the disease (Canadian Diabetes Association, 2007). Given that the First Nations population in British Columbia is generally young, with a median age of 24.7 years compared to 37.7 in non-Aboriginal populations (Figure 6) (Statistics Canada, 2003), and that D2 progresses in frequency with age (Figure 4), the proportion of First Nations people diagnosed with D2, and the future health costs associated with the disease in this population, will only continue to escalate.



**Figure 6.** Percent of British Columbia Aboriginal and non-Aboriginal people in 4 age categories (age 0-14, 15-24, 25-54, 55+). (Figure adapted from Ministry of Health Planning, Provincial Health Officer, 2002)

In order to identify the specific PA needs of First Nations youth in British Columbia, researchers need to examine the impact of PA on important metabolic measures such as IR. IR is the key measure used to identify an individual's risk of health complications related to D2. It is the common link among the risk factors for D2 (obesity, hypertension, dyslipidemia, hyperinsulinemia, family history of D2, ethnic minority, puberty) and warrants special attention (Arslanian, 2002).

Research examining the effects of PA on IR in youth is still in its early stages. Some aerobic exercise training studies have reported decreases in body fat and concomitant reductions of IR in children and adolescents (Nassis et al., 2005; Kang et al., 2002; McMurray, Bauman, Harrell, Brown, & Bangdiwala, 2000). Compliance with structured exercise training programs that aim to improve health and fitness among youth is difficult to achieve however. Furthermore, the vast majority of children and adolescents do not value the long-term health benefits of exercise (Olga, Salguero, Conception & Aduarde, 2006). Physical activities,

therefore, that can be incorporated into daily routines and are fun, rather than prescriptive exercises that emphasize health and fitness, might be more effective in establishing healthy behaviours and accruing long-term health-related benefits in First Nations youth.

Relatively few studies have investigated how habitual PA influences IR in youth. Ku et al. (2000) and Schmitz et al. (2002) investigated this relationship using subjective questionnaires and interviews to determine habitual PA. While there are benefits of using subjective methods to measure PA (i.e. qualitative aspects such as intensity, type, weight bearing), it is recommended that in children 11 years old or younger, self-report methods are not used (Brage et al., 2004). They are thought to be inadequate for use in children because of cognitive limitations and because children often engage in short but frequent bouts of unstructured activities that are difficult to recall and describe. As a result, studies have started using direct or objective measures to determine habitual PA (Krekoukia et al., 2007; Anderson et al., 2006; Brage et al., 2004; Bunt, Salbe, Harper, Hanson, & Tataranni, 2003). Despite the growing pool of studies investigating the relationship between objectively measured habitual PA and IR in ethnic minorities, no study, to our knowledge, has investigated it in a population of First Nations youth.

The Public Health Agency of Canada offers 'one size fits all' PA recommendations for youth (90 minutes of moderate to vigorous PA per day) (Health Canada and the Canadian Society for Exercise Physiology, 2002a; Health Canada and the Canadian Society for Exercise Physiology, 2002b), even though it is suggested that First Nations youth, along with other minority youth, may require

different amounts of PA for health benefits (Goran, Bergman, Cruz, & Watanabe, 2002). More appropriate recommendations are urgently needed. Knowing the relationship between PA and IR in First Nations youth will help guide the development of PA recommendations for First Nations children and adolescents in BC.

There are many differences between First Nations communities in Canada. Despite these differences, First Nations groups are closer genetically than Caucasian groups making this research more appropriate for First Nations youth than similar studies in Caucasian groups.

This type of thoughtful research will also help focus chronic disease prevention strategies, potentially curbing the development of D2 in First Nations communities and ultimately reducing the socioeconomic impact of D2 in Canada. Determining the dose-response relationship between objectively measured habitual PA and IR is a big step in the right direction.

### *Purpose*

Pubertal IR can tip the scale towards full blown D2 in at-risk youth. Not surprisingly, the diagnosis of D2 in children usually occurs at around the time of mid-puberty (~13.5 yrs). Unfortunately, once diagnosed, diabetes is most often a lifelong condition. A limited number of studies have used objective measures to examine the association between habitual PA and IR in youth. First Nations youth are especially susceptible to IR and D2. No study, however, has examined the relationship between habitual PA and IR in First Nations youth. This study will

identify the relationship between daily PA and IR in First Nations youth in Hartley Bay and Kitkatla, 2 remote coastal villages in northern British Columbia. Identifying the impact of habitual PA on IR in this vulnerable group will help define more appropriate PA recommendations. Such recommendations will prove to be increasingly more important as a generally young First Nations population ages.

*Research questions*

1. Does total daily physical activity influence insulin resistance in First Nations youth?
  - a) Is objectively measured average physical activity intensity associated with insulin resistance in First Nations youth?
  - b) Is the association different among gender, adiposity, physical activity and pubertal subgroups?
  - c) If an association exists, is it independent of confounding factors such as gender, age, pubertal status, total adiposity, central obesity, cardio-respiratory fitness and diet?
  - d) If an association exists, is it different than those reported in similar Caucasian studies?
2. Does habitual moderate to vigorous physical activity influence insulin resistance in First Nations youth?
  - a) Is objectively measured total daily moderate to vigorous physical activity associated with insulin resistance in First Nations youth?

b) Is the association different among gender, adiposity, physical activity and pubertal subgroups?

c) If an association exists, is it independent of confounding factors such as gender, age, pubertal status, total adiposity, central obesity, cardio-respiratory fitness, and diet?

d) If an association exists, is it different than the association between total daily physical activity and insulin resistance?

### *Definitions*

- 1) Aboriginal: A number of terms are used in referring to the Indigenous population of Canada. It is important to understand the origin and definition of these terms, because each group of Aboriginal people has a distinct history, culture, and legal entitlements. In addition, much of the current data about Aboriginal people refer only to specific Aboriginal groups. Aboriginal people are the descendents of the original inhabitants of North America. The Constitution Act recognizes 3 groups of Aboriginal peoples: First Nation, Inuit and Métis. The focus of this study was the relationship between PA and IR in First Nations youth.
- 2) Adolescent: Pubertal (i.e. Tanner stage 2 to 4)
- 3) Body Mass Index: A crude estimate of total adiposity; body mass (kg) divided by height squared ( $m^2$ ).
- 4) Caucasian: White European descent.
- 5) Child: Pre-pubertal (i.e. Tanner stage 1)

- 6) Diabetes Mellitus: A complex disorder of carbohydrate, fat, and protein metabolism resulting from a lack of insulin secretion (type 1) or defective insulin receptors (type 2).
- 7) First Nation: The term 'First Nation' is used as an adjective, as in 'First Nations people', and as a noun, as in the 'Garden Hill First Nation' (Dean, 1998).
- 8) Insulin Resistance or Insulin Sensitivity: Resistance or sensitivity of liver, fat and muscle cells to the actions of insulin that help control blood glucose levels.
- 9) Obese: Excessive amounts of body fat relative to body weight. The term obese is not synonymous with overweight. International BMI cut-off points for determination of obesity for 9 to 12 year old boys and girls range from 22.77 and 22.81 kg/m<sup>2</sup> to 26.02 and 26.67 kg/m<sup>2</sup> respectively (Appendix 1) (Cole, Bellizzi, Flegal, & Dietz, 2000).
- 10) Overweight: International BMI cut-off points for determination of overweight for 9 to 12 year old boys and girls range from 19.10 and 19.07 kg/m<sup>2</sup> to 21.22 and 21.68 kg/m<sup>2</sup> respectively (Appendix 1) (Cole et al., 2000)
- 11) On-reserve: Refers to all members of a specific First Nation living on their home reserve (Dean, 1998b).
- 12) Oral glucose tolerance test (OGTT): The administration of glucose orally to determine how quickly it is cleared from the blood. The test is used to test for diabetes and IR.

- 13) Tanner Staging: Method of defining pubertal stage based on external primary and secondary sexual characteristics such as the size of breasts, genitalia and development of pubic hair.
- 14) Youth: Term used in this study referring to both pre-pubertal children and pubertal adolescents.

*Potential Significance of the Research*

- 1) **Practicality**: This study will provide in depth knowledge of a modifiable factor that affects IR in First Nations youth. The study findings will aid in designing more effective PA programs for the prevention of D2 and enhancing general health.
- 2) **Addressing the knowledge gap**: A limited number of studies have examined the impact of habitual PA on IR in children and adolescents. No study that we know of has examined this in First Nations youth.
- 3) **Adding to the understanding of a phenomenon**: It is evident that First Nations people are prone to IR and D2. It is not clear however whether they need to engage in more, less or the same amount of PA than their Caucasian counterparts for the same health benefits.

## Chapter 2: Literature Review

The purpose of this literature review is to place the research questions directing this study into the context of previous PA research as well as to identify important findings, study limitations and gaps in the body of knowledge. The literature review is divided into 4 sections. First, a general overview of type 2 diabetes (D2) helps explain paediatric and First Nations susceptibility to the disease as well as the burden of D2. The second section will describe physiological mechanisms through which adiposity, diet and PA independently affect IR in children and adolescents. Third, research exploring the relationship between PA and IR in youth will be considered. Lastly, research exploring the validity of the current measurement tools as well as other issues relating to these tools is discussed.

### *2.1 Type 2 Diabetes Mellitus: Overview and Susceptibility*

#### a) Overview

##### *i) Definition*

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia (fasting plasma glucose greater than or equal to 7.0 mmol/L after an overnight fast) (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003) (Appendix 2). There are several etiologic classifications of diabetes. The most common are type 1, type 2 and gestational diabetes. Other specific types include rare monogenetic defects of either pancreatic  $\beta$ -cell function or of insulin action, primary diseases of the endocrine pancreas, or drug-induced diabetes (Greenspan & Gardner, 2004). D2 accounts for most of the diabetic cases in Canada, nearly 90%

(Canadian Diabetes Association, 2007). It is a heterogeneous disorder resulting from a combination of IR and inadequate insulin secretion (Silverthorn, 1998).

*ii) Pathophysiology*

D2 results from the interaction of several genetic and environmental factors. Ethnicity, sex, genetic factors, birth weight, socioeconomic status, guardian smoking, obesity, central obesity, physical inactivity, puberty, and age have all shown to affect the development of the disease. In individuals with normal glucose tolerance insulin activates receptor sites on cell membranes and initiates the translocation and insertion of the GLUT-4 transporters into the cell membrane. This allows cells to take up glucose from the blood by facilitated diffusion. When cells are resistant to the actions of insulin however (i.e. due to a genetic defect and/or because they are over-nourished), glucose cannot enter the cell and hyperglycemia develops. In response to elevated blood glucose levels the  $\beta$ -cells of the islets of Langerhans in the endocrine pancreas compensate by increasing production and secretion of insulin. In severe cases, exposure to prolonged fasting hyperglycemia results in a progressive decline in  $\beta$ -cell function or even  $\beta$ -cell exhaustion. This phenomenon has been called 'desensitization' or 'glucose toxicity'. The end result is clinical, often irreversible and life-threatening D2. The pathophysiology for the development of the disease proposed by Goran, Ball & Cruz (2003) is illustrated in Appendix 3.

### *iii) Prevalence*

An important component of the description of D2 in First Nations youth is an estimation of the prevalence of the disease in the adult population. Although clinical diabetes may not be apparent in children in some First Nations communities, identifying the prevalence in adults helps assess the impact of the cultural shifts towards inactivity and obesity and predict future metabolic challenges for children.

D2 prevalence has increased in frequency in adult Aboriginal populations (Retnakaran, Hanley, Connelly, Harris, & Zinman, 2006). In the past 2 decades a rapid increase in prevalence has been documented. In the Sioux Lookout Zone of north-western Ontario the prevalence increased by 45% between 1984 and 1994 (Young et al., 2000). In Saskatchewan the rate doubled between 1980 and 1990 (Young et al., 2000). The prevalence rate of diabetes in the Oji-Cree of Sandy Lake in northern Ontario (26.1%) (Harris et al., 1997) is among the highest in the world (Dean et al., 2003).

The age- and sex-specific prevalence rates of self-reported diabetes from the 1991 Aboriginal Peoples Survey and the 1999 First Nations and Inuit Regional Health Survey together with all-Canadian data from the 1994 National Population Health Survey highlight the disparity between Aboriginal and non-Aboriginal Canadians (Figure 4). When age-adjusted to the Canadian population, the prevalence of D2 was 3.6 and 5.3 times higher among Aboriginal men and women respectively than among all Canadian men and women.

The overall prevalence of diabetes in on-reserve status BC First Nations youth and adults in 1997 was 2.6% - more than double the 1.2% prevalence in 1987

(Johnson, Martin, & Sarin, 2002). Given that the diagnostic criteria were recently lowered by an international committee of diabetes experts (from 7.8 to 7.0 mmol/L fasting plasma glucose) (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997), the current prevalence is likely even higher.

Data from the United States suggest a 10 to 30 fold increase in the number of children with D2 over the past 10 to 15 years (Fagot-Campagna, 2000). While clinicians started recognizing D2 in North American Caucasian, African American, Asian American and Hispanic children in the 1990's, D2 was first acknowledged in American Indian and First Nations paediatric populations more than a decade earlier in the late 1970's and early 1980's suggesting that Aboriginals are particularly susceptible to the disease (Fagot-Campagna, 2000). Since D2 was first recognized in Canada in Oji-Cree children in 1983 (Dean et al., 2003), numerous population-based D2 youth screening studies have been conducted in Canada. Several studies have determined that the prevalence of affected children has increased in Manitoba and north-western Ontario (Dean et al., 2003; Hegele et al., 1999a; Harris, Perkins, & Whalen-Brough, 1996; Dean, Mundy, & Moffatt, 1992). Additionally, the number of new cases referred to the Manitoba Diabetes Education Resource for Children and Adolescents has increased from 4 per year in 1986 to 35 per year in 2001 (Dean et al., 2003) suggesting that the disease is more prevalent (Figure 3). The effect of increased awareness of community members, family members and healthcare professionals on the reported incidence of the disease cannot be ruled out.

This trend is not consistent across all Canadian First Nations communities however. In the early years of D2 screening studies in First Nations youth, no cases

of diabetes in youth 15 to 19 yrs were found in 2 Cree communities in western Quebec (Delisle & Ekoé, 1993). In 1999, no cases of diabetes were diagnosed in 400 Cree 10 to 19 yr old youth in 2 northern Quebec communities (Dannenbaum et al., 1999). Similarly, in 2000, no cases of diabetes were found in 115 5 to 19 yr old Ojibway youth in Christian Island First Nations in southern Ontario (Smith, Gowanlock, & Babcock, 2001).

Despite the dramatic increase in public awareness of D2, reports of the disease among children and adolescents are not consistent across Canada. Indeed, the prevalence of diabetes has been found to vary according to language group, culture area, geographic location and degree of isolation, both nationally and regionally (Johnson et al., 2002). For example, in 1995, the prevalence of D2 among adults in 2 large Algonquin communities in Quebec was enormously different (Delisle, Rivard, & Ekoé, 1995). In men, the prevalence was 23.9% versus 16.3%, and in women they were 48.6% versus 23.9%. Also, between 1996 and 2000 in Manitoba, 80% of type 2 diabetic First Nations youth lived in a remote or rural community whereas only 20% lived in or near an urban centre (Dean et al., 2003).

Although the D2 trend in First Nations youth is not uniform across Canada, high rates of obesity and IR in First Nations children (Young et al., 2000) and high rates of the disease in adults both raise concerns about the future prevalence of D2 and CVD in this population.

#### *iv) Costs*

The burden of diabetes due to health care costs, disability, work loss, and premature death in Canada is approximately \$40 billion annually (Canadian Diabetes

Association, 2007). This number will only continue to increase as a generally young First Nations population ages. Price-tags, however, cannot be placed on quality of life issues for those living with diabetes. The short-term symptoms of D2 include polyuria (excessive urination), thirst, recurrent blurred vision, paresthesia (numbness and/or tingling on skin), chronic skin infections and fatigue. The long-term complications of diabetes are serious. They include CVD (i.e. strokes and heart attacks), neuropathy (i.e. impaired sensation and pain in feet and hands, impotence, amputation), retinopathy (i.e. progressive loss of vision), and nephropathy (i.e. kidney failure) (Greenspan & Gardner, 2004). Despite the severity of these consequences, relatively few studies have investigated ways of improving risk factors for D2 in children (Krekoukia et al., 2007).

b) Susceptibility

*i) Children and Adolescents*

Although the risk factors for the development of the disease in adults and children are similar (i.e. increased body fat and decreased PA), the time course is accelerated in children (Goran et al., 2003). In adults it can take decades for diabetes to develop. In children and adolescents, the disease can develop in just a few years. The components of the multiple metabolic syndrome (obesity, hypertension, hyperinsulinemia and dyslipidemia) which often precede clinical D2, have been shown to cluster in children as young as 8 yrs of age (Froberg & Andersen, 2005). Moreover, First Nations children as young as 8 yrs old have been diagnosed with D2 in northern Manitoba (Young et al., 2000a).

The reasons for D2 susceptibility early in life are unclear however. A possible explanation is that the immature endocrine pancreas is unable to adequately compensate through increased  $\beta$ -cell secretion for greater tissue resistance to insulin (Goran et al., 2003). On the other hand, it is well documented why children entering puberty are at an increased risk of D2. Several studies have shown that IR increases dramatically, by approximately 30%, at the onset of puberty (Tanner Stage 2), regardless of sex, ethnicity and obesity, and returns to close to pre-pubertal levels at maturity (Figure 5) (Moran et al. 1999). This pubertal IR often tips the scale towards D2 during adolescence. Unfortunately, once D2 is diagnosed it is usually a life-long disease. The mechanisms and reasons for this transient stage of IR are not clear, although it is hypothesized that pubertal IR likely plays a role in healthy somatic growth (Goran & Gower, 2001). For this reason, it may not be prudent to try to prevent the pubertal increase in IR. Instead PA interventions should be explored for decreasing body fat and IR before pubertal development, especially in children who belong to high-risk ethnic groups and are prone to high levels of IR. The time before puberty truly is a window of opportunity for the prevention of future health complications.

*ii) First Nations people*

Environmental factors have played an important role in the emergence of D2 in First Nations populations. In the last half century, First Nations people have changed their diets and PA patterns to fit an industrialized lifestyle model. Many First Nations people now derive most of their diet from high calorie Western foods and live sedentary and physically inactive lives (First Nations Information

Governance Committee, 2005). As a result, overweight and obesity rates have soared and the prevalence of IR and D2 has increased. Weiss (1984) coined the term “New World Syndrome” to describe the co-occurrence of obesity and diabetes among Native Americans (Young, Chateau, & Zhang, 2002).

In addition to changing behaviours and environments, there is strong evidence that genetic factors predispose some ethnic groups to D2. For instance, epidemiological studies have reported familial clustering of D2 (Ehtisham, Crabtree, Clark, Shaw, & Barrett, 2005). In Canadian Oji-Cree, genome-wide scanning for diabetes susceptibility among affected sibling pairs revealed 4 markers suggestive of association with diabetes (Hegele et al., 1999a). There is also a high concordance rate for monozygotic (identical) twins (50 to 80%). Lastly, the prevalence of D2 varies in different parts of the world, ranging from 2 to 5% in Europe to more than 50% in Pima Indians in Arizona further suggesting a genetic component to the disease (Greenspan & Gardner, 2004).

The emerging D2 epidemic appears to be affecting mostly youth from minority ethnic groups. African American, Pima Indian, South Asian, Hispanic, and New Zealand Maori, for example, have exhibited higher insulin levels, which is indicative of greater IR, compared with their Caucasian peers (Ehtisham et al., 2005; Arslanian, 2002; Kang et al., 2002; Goran, 2001; Ku, Gower, Hunter, & Goran, 2000; McGrath, Parker, & Dawson, 1999). Several studies have also reported higher fasting insulin levels and IR in First Nations versus Caucasian children (Moore, Copeland, Parker, Burgin, & Blackett, 2006; Dean, Young, Flett, & Wood-Steiman, 1998). It appears then that children of particular ethnic origins are prone to IR. In the

presence of certain environmental factors (i.e. chronic physical inactivity) this susceptibility increases the risk of D2 and often results in the manifestation of the disease.

Relatively little is known about the genes contributing to common forms of D2. The ‘thrifty gene’ theory, first postulated in the 1960’s, attempts to explain the high prevalence of obesity and D2 in ethnic populations (Neel, 1962). This theory proposes that ethnic groups are genetically predisposed to store energy very efficiently as a result of their ancestor’s nomadic lifestyles when food supplies were unpredictable and scarce. In times of food shortage, for example, the ‘thrifty genotype’ enabled the rapid production and secretion of insulin in response to rising blood glucose levels, which facilitated the storage of glucose in the form of triglycerides in fat cells. With the adoption of a more Western lifestyle and a continuous and ample food supply, the quick insulin response results in hyperinsulinemia, hyperglycemia, obesity and eventually D2. Such a metabolic phenotype has become a clear disadvantage.

While most experts believe that genetics play a major role in the high prevalence of D2 among First Nations people, a specific gene or combination of genes responsible for D2 has not yet been identified. The consensus is that D2 is a multi-factorial disease composed of highly genetic forms at one end of the spectrum and forms strongly related to environmental factors at the other (Froguel, 1997). This has made it extremely difficult to find a gene or group of genes responsible for the disease. According to Froguel (1997), the existence of overlapping

pathophysiological features, such as hypertension and obesity, and the interference of environmental risk factors have also made it difficult to study D2 genes.

Despite these limitations, some progress in identifying genes and genetic variations that predispose some ethnic groups to D2 risk factors such as obesity and IR have been made. For example, single gene mutations in leptin and its receptor have been shown to cause obesity (Terán-García & Bouchard, 2007). First Nations people are prone to D2 in part because of their susceptibility to obesity, particularly central obesity (Harris et al., 1997). As obesity and IR ‘genes’ are identified, knowledge of the pathophysiology of D2 development will be enhanced.

There is also evidence that mechanism for maintaining euglycemia (glucose levels in the normal range) may differ in different ethnic groups. For example, the compensatory response to IR has been shown to vary in African American versus Hispanic children. In a 2002 study, African American children responded to IR by reducing the amount of insulin extracted by the liver, and Hispanic children responded by increasing the secretion of insulin (Goran et al., 2002). It has also been suggested that the contribution of total body fat versus visceral fat to IR may be different in different ethnic groups (Cruz, Bergman, & Goran, 2002). A final example comes from a finding that indicated that the effect of low birth weight on fasting insulin was more harmful in African American children than in Caucasian children suggesting that African Americans may be more prone to poor fetal growth, and thus, IR (Li, Johnson, & Goran, 2001).

These examples suggest that the mechanisms for maintaining euglycemia and the underlying pathophysiology leading to D2 may be different for First Nations

groups as well. More studies on the potential influence of habitual PA on glycemic control and IR among First Nations people are needed.

## *2.2 Influence of adiposity, diet and physical activity on insulin resistance and the development of type 2 diabetes*

### a) Adiposity

Adiposity has the most significant influence on fasting insulin levels and IR of all the risk factors for D2 (McMurray et al., 2000). High amounts of stored fat and abnormal adipose tissue metabolism likely play major roles in the development of D2. Four components of fat storage and adipose tissue metabolism including atypical tissue biology, excess fat mass, high level of abdominal fat and ectopic or abnormal fat distribution, may be relevant to the development of D2 (Terán-García & Bouchard, 2007).

Impaired regulation of adipose tissue biology, such as interrupted pre-adipocyte differentiation into mature adipocytes, is typical in obese individuals and may promote IR. Also, altered production and secretion of adipokines from adipocytes (i.e. retinol binding protein-4, fatty-acid binding protein) have physiological and metabolic consequences that tend to promote obesity, IR and D2. These observations are not consistent across all studies however (Terán-García & Bouchard, 2007).

Increased fat mass has also been associated with IR and the development of D2 (Terán-García & Bouchard, 2007). Generally, larger fat cells have increased rates of triglyceride synthesis, lipolysis and transmembrane fatty acid flux. As fat cells

increase in size, the concentration of adipokines (i.e. leptin) and polypeptides (i.e. C-reactive peptide) secreted by adipose tissues into the blood also increase, influencing hepatic lipoprotein metabolism and endothelial function. Also, larger adipocytes progressively lose their ability to store fat and contribute to higher circulating free fatty acid levels. Excess fat mass is likely the single-most important cause of IR and D2 as suggested by the association between the increase in obesity prevalence and obesity-related morbidities (Terán-García & Bouchard, 2007).

A potential mechanism explaining the link between high visceral fat and elevated fasting insulin is through its effect on hepatic insulin clearance. It is postulated that exposure to free fatty acids by the liver may decrease hepatic insulin clearance and increase fasting insulin levels (Goran, Bergman, Gower, 2001). This is particularly important in Aboriginal peoples as they store fat more centrally than Caucasian cohorts (Lohman et al., 2000; Potvin et al., 1999; Harris et al., 1997). This is characterized by a high waist-to-hip ratio (Harris et al., 1997).

These components of fat storage and metabolism favour the development of IR especially in the presence of a genetic predisposition and an unhealthy lifestyle.

#### b) Diet

Changes in the amount and kind of calories consumed can play a large role in avoiding IR and D2. It is proposed that the increase in the amount of carbohydrate (CHO) in a typical Western diet, coupled with a change to high-glycemic-index CHO's (simple, refined sugars) may be the most important contributor to the paediatric obesity epidemic (Slyper, 2004).

CHO's are usually categorized as simple sugars or complex CHO's. It has become common practice to classify CHO's in terms of their glucose and insulin responses, or their "glycemic index" (Slyper, 2004). The "glycemic index" reflects the ease with which a CHO is digested compared to glucose or white bread. In general, starches made up of whole grains have low glycemic indices, as do whole beans and most green vegetables. Numerous studies have shown that low-glycemic-index or high-fibre diets consistently lead to lower glucose and insulin profiles compared with isocaloric high-glycemic-index or low fibre diets (Slyper, 2004). Correspondingly high-glycemic-index CHO's, including but not limited to fruit drinks, soft drinks, cakes, cookies and white potatoes are associated with a greater release of insulin and glucose into the blood after a meal which can lead to excessive weight gain, especially in susceptible children (Slyper, 2004).

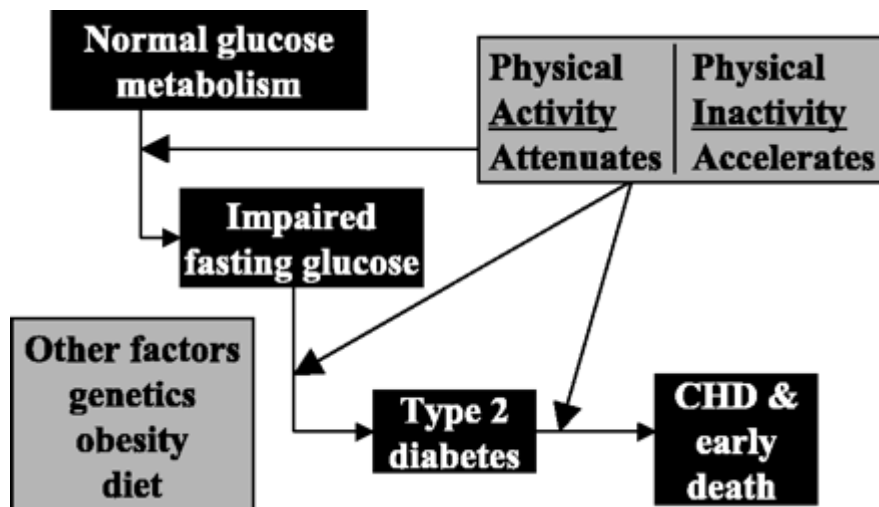
Diets restricted in high-glycemic sodas and juices and containing ample whole grains, vegetables, and fruit can improve insulin profiles and reduce the risk of D2 in males and females of all ages.

c) Physical activity

PA refers to "behaviour, specifically a body movement that occurs from skeletal muscle contraction and results in increased energy expenditure above resting metabolic rate." (LaMonte, Blair, & Church, 2005). Physical training, on the other hand, is a type of PA that is performed with the intention of enhancing components of physical fitness, such as aerobic power, muscular strength and muscular endurance.

Several studies have examined the association between cardio-respiratory fitness (CRF) and D2. Studies investigating the association between habitual PA and IR or D2 are less common. These studies are particularly interesting since habitual PA, the principle determinant of aerobic power (LaMonte et al., 2005), is generally related to lower IR and a healthy metabolic profile, while studies using aerobic power as the main outcome are less conclusive (Goran et al., 2003). Other determinants of CRF, including age, sex, health status and genetics, likely contribute to the inconsistent findings. Few large prospective studies have been conducted that support the relationship between other components of physical fitness (i.e. muscular strength) and D2. In one of the few studies examining the effect of strength training on metabolic risk in a paediatric population, resistance training performed for 20 minutes, 3 days a week for 5 months led to increases in strength, improvements in glucose tolerance and insulin levels that approached significance, and stopped visceral fat accumulation (Treuth, Hunter, Figueroa-Colon, & Goran, 1998). While the group increased in total body fatness, the gain was not accompanied by an increase in visceral fat. A strength training intervention could potentially benefit First Nations youth in particular because of their tendency to store fat centrally.

LaMonte *et al.* (2005) contend that physical inactivity is the “most proximal behavioural cause of IR” and that PA can attenuate the development of D2 at several stages in the progression of the disease (Figure 7).



**Figure 7.** Schematic of the relation of physical activity with the progression from normal glucose metabolism to clinical diabetes and coronary heart disease. (From LaMonte et al., 2005)

The mechanism through which PA improves IR and glucose homeostasis is a primary focus in current health research and has yet to be well elucidated. The current consensus however is that PA improves insulin action and glucose control through numerous mechanisms involving the skeletal muscle (the primary target tissue for insulin action), adipose tissue, liver and endothelium.

Exercising muscles require metabolic fuel and this need is partially met through increased glucose uptake and utilization. The circulatory response (i.e. increased blood flow associated with exercise) is therefore an important regulatory response to exercise. The pumping action of skeletal muscles and arteriolar dilatation are primarily responsible for increasing blood flow to contracting muscles (Rowland, 2005). Although neural control mechanisms may be involved, it is believed that chemical factors (i.e. potassium and hydrogen ions, nitric oxide and lactate) and tissue hypoxia elicit the vasodilatory effect within the working muscle (Goodyear &

Kahn, 1998). As blood flow increases, so does the availability of insulin and glucose to skeletal muscles. Consequently, glucose availability is usually not the rate-limiting factor of glucose utilization during exercise. Rather, glucose transport is believed to be the rate-limiting step (Goodyear & Kahn, 1998).

Insulin and muscle contractions stimulate glucose transport during exercise. Although the signalling pathways are distinct, both insulin and muscle contractions lead to the translocation of GLUT4 glucose transporter proteins from intracellular pools to the plasma membrane and transverse tubules resulting in increased glucose uptake (Goodyear & Kahn, 1998). Insulin-stimulated glucose uptake involves insulin receptor substrate-3 and phosphatidylinositol 3-kinase (PI 3-kinase) and the redistribution of Rab4 protein. Exercise is believed to increase insulin binding, but more importantly key proteins in the insulin cascade, including PI 3-kinase, resulting in enhanced insulin action (Brage et al., 2004).

Muscle contractions, on the other hand, utilize PI 3-kinase and mitogen-activated protein kinase-independent mechanism, and do not result in the redistribution of Rab4 (Greenspan & Gardner, 2004). The translocation signal is likely initiated by the release of calcium from the sarcoplasmic reticulum (leading to the interaction of actin and myosin filaments during muscle contraction) and may involve autocrine/paracrine mechanisms (i.e. nitric oxide, bradykinin), protein kinase C, or a combination of these and other unknown factors (Goodyear & Kahn, 1998).

Also, it is suggested that the depletion of muscle glycogen with higher intensity aerobic exercise may enhance the acute effects of exercise on insulin action (Kelley et al., 1999). Notably, the acute improvements in IR and glucose control

with exercise can last for several hours following the cessation of activity (Goodyear & Kahn, 1998).

PA may influence IR and glucose control over the long-term as well. Regular PA or training may increase fat-free mass, which increases the volume of skeletal muscle tissue into which glucose can be transported (Schmitz et al., 2002). Also, regular PA may increase skeletal muscle capillarization and blood flow as well as the number of highly oxidative and insulin-sensitive type IIa and type I skeletal muscle fibres. As well, habitual PA may enhance fat oxidation and improve muscle glycogen synthase activity to replenish glycogen used during exercise (Krekoukia et al., 2007; LaMonte et al., 2005; Brage et al., 2004). PA may also decrease the amount of skeletal muscle and blood lipid content which could impair insulin action (Krekoukia et al., 2007; LaMonte et al., 2005; Brage et al., 2004). Additionally, exercise may decrease excessive hepatic secretion of glucose and very-low density lipoproteins (LaMonte et al., 2005).

Thoughtful and appropriate interventions that promote PA (as well as decrease physical inactivity) are valuable because they have the capacity to influence several important physiological outcomes including body fat, IR and blood lipids and attenuate the development of D2 and CVD without the use of drugs or the implementation of a strict diet.

### *2.3 Physical activity and insulin resistance: Is there a relationship?*

#### a) Adults

There is an extensive body of intervention and cross-sectional research based evidence supporting the hypothesis that a physically active lifestyle prevents adverse changes in glucose homeostasis and substantially delays the progression from impaired glycemic control to clinical diabetes (LaMonte et al., 2005). The relationship between PA and IR has been examined in several studies in adults (Laaksonen et al., 2002; LaMonte et al., 2005).

We know of one study that has examined this relationship in First Nations adults (Kriska, Hanley, Harris, & Zinman, 2001). Kriska et al. (2001) found that subjectively measured PA is independently associated with fasting insulin concentrations, after controlling for age, body mass index (BMI) or percent body fat, and waist circumference in First Nations Oji-Cree. The suggestion that a physically active lifestyle improves IR in an adult First Nations population separate from any influence on body composition is consistent with the existing literature in adults (Kriska et al., 2001).

#### b) Children

##### *i) Intervention Studies*

There are a limited but increasing number of research studies that have examined the relationship between physical training and IR in children. In the past decade several trials have demonstrated improvements in IR following exercise intervention programs in children (Kahle et al., 1996; McMurray et al., 2000; Kang et al., 2002; Nassis et al., 2005). While the trials may vary in participant

characteristics (i.e. age, pubertal stage, sex, and degree of adiposity) as well as on the measures for IR and adiposity, the findings are generally uniform.

One of the first large scale intervention studies in normal weight children was conducted by McMurray et al. (2000). They found that in normal weight 11 to 14 year old children, participation in an aerobic exercise program that increased aerobic power resulted in lower circulating levels of insulin independent of changes in body fat. McMurray et al. (2000) also found that the benefits may be reserved for those with initially elevated resting insulin levels, a finding that is consistent with other studies in adults and that was confirmed in a paediatric study 2 years later (Kang et al., 2002). This finding is logical, since children who have low baseline measures of insulin cannot improve as much as those who have already high levels. This ‘floor effect’ also helps explain why most studies of obese children find an effect of exercise on insulin levels, while the results of studies of normal weight children are not as consistent (McMurray et al., 2000).

For improvements in insulin levels to occur McMurray et al. (2000) suggest that exercise programs must improve aerobic power. This study stands in stark contrast to Kahle et al.’s (1996) study that found that mild, routine exercise improves insulin levels in adolescents without changes in aerobic power or percent fat. Studies in adults have also shown that moderate intensity activities can improve insulin sensitivity (Mayer-Davis et al., 1998). The reason for this discrepancy may lie in the notion that benefits are usually seen in populations with unfavourable baseline values. In McMurray et al. (2000) the “No Change in Fitness” group had baseline VO<sub>2</sub> max values that were higher than the “Improved Fitness” group baseline values

( $p < .001$ ). This implies that the “Improved Fitness” group was more likely to benefit from the exercise due to the fact that they had more ‘room’ to improve. We suggest that it was not the improvement in fitness that necessarily mediated the positive change in insulin levels, but rather the extra ‘room’ for improvement in the “Improved Fitness” group.

Kang et al. (2002) tested the hypothesis that aerobic training would improve IR in obese adolescents. They found that aerobic training, especially vigorous-intensity aerobic training, had a favourable effect on fasting insulin in obese adolescents, but this effect was not independent of body fatness. Although Kang et al. (2002) suggest that vigorous-intensity aerobic training is especially effective in reducing fasting insulin levels they could not make conclusive statements, as they failed to achieve an adequate margin between the moderate and high-intensity physical training groups.

Kang et al. (2002) also determined that African American youth had significantly higher insulin change scores than Caucasian youth (37.65 versus 16.31 pmol/L respectively,  $p = 0.017$ ) suggesting that aerobic training had a greater influence on IR in African American compared to Caucasian youth. It is not clear if this occurred because the African American youth had higher fasting levels of insulin initially or if PA has a greater impact on IR in all African American youth. Baseline insulin concentrations for Caucasian boys in this study were lower, albeit not significantly, than concentrations in African American boys (157.34 versus 135.2 pmol/L), suggesting that differences in baseline characteristics explain the study

findings. Whether the strength of the association between aerobic training and IR varies between ethnic groups remains unknown.

Nassis et al. (2005) provide strong support for the suggestion that increased PA may reduce IR through mechanisms other than through a reduction in body adiposity (i.e. changes in the ability of muscles to metabolize glucose). They found that 12 weeks of aerobic training improved insulin sensitivity in overweight and obese girls without changes in body weight or percent body fat. This finding is consistent with that of others with adults (Duncan et al., 2003) and in children (Kahle et al., 1996).

Kelly et al. (2004) found that fasting insulin displayed a trend toward improvement after an 8 week aerobic exercise intervention, although they found no change in glucose concentration after a glucose tolerance test in 11 yr old overweight boys. This suggests that while insulin levels in the blood decreased, insulin sensitivity did not improve through the trial. This finding is inconsistent with those in similar studies. The authors offered that a small sample size may explain the failure to observe a change in IR. Eight weeks of training may have also been insufficient to elicit a significant change.

In contrast to several studies, Gutin et al. (1996) found no significant change in fasting insulin after 10 weeks of exercise training in 24 obese African American girls (Gutin, Cucuzzo, Islam, Smith, & Stachura, 1996). This may be explained by compensatory behaviour, since only self-reported vigorous PA and not overall volume of activity was increased. It is likely that while the participants increased the amount of high-intensity PA they performed they also decreased the amount of low-

to moderate-intensity activity they did, removing the benefits of increased vigorous activity.

From the 6 studies reviewed with similar characteristics, 5 found that physical training improves indices of IR in children. Three of these studies found that exercise improves IR in the absence of changes in body composition (Ku et al., 2000; McMurray et al., 2000; Nassis et al., 2005) and 2 suggest that vigorous-intensity aerobic physical training improves insulin levels in youth more so than low- or moderate-intensity exercise (McMurray et al., 2000; Kang et al., 2002;). An additional study of youth found that mild, routine PA improves insulin sensitivity as well (Kahle et al., 1996). Two studies determined that the greatest improvements occur in individuals with already high insulin levels (McMurray et al., 2000; Kang et al., 2002). Thus, physical training, particularly vigorous-intensity training, improves IR in children, especially children with unfavourable baseline insulin values. The beneficial influence of physical training on insulin action, and thus on reduction of D2 risk, appears to be operative in childhood. To our knowledge it is unclear whether physical training affects IR differently in ethnic groups. Although this relationship has been examined in Caucasian and African American children, differences have not been identified. No longitudinal study has examined this relationship in Native American or First Nations youth.

#### *ii) Cross-sectional studies*

A limited but growing number of cross-sectional studies have investigated the association between PA and IR in children (Krekoukia et al., 2007; Brage et al., 2004; Bunt et al., 2003; Schmitz et al., 2002; Ku et al., 2000) The advantage of

studying this relationship by cross-section is that the studies are not limited by a short exposure to a PA program (8 to 12 weeks). In children, as in adults, there are high and low responders to exercise as well as early and late responders. Some intervention studies may not be long enough to elicit a significant response in low and late responders thus tainting study findings. The main drawback of cross-sectional studies is that they only provide a snapshot of what is actually occurring. Therefore errors in measurement, in determining habitual PA for example, can skew findings. This is a major reason why accurate objective measures of PA, such as that collected from accelerometers, are so valuable to contemporary PA research.

Krekoukia et al. (2007) found that total and central adiposity, were positively and significantly correlated to an index of IR (homeostasis model estimate of insulin resistance or HOMA-IR) ( $r = .56$ -.73,  $p < .01$ ) in fifty 9 to 11.5 year old obese and lean Greek children, whereas PA, measured by accelerometry, presented a tendency for correlation ( $r = -0.22$ ,  $p = .07$ ). In the multiple regression model, total PA (min/day) and waist circumference (cm) were associated with IR, after adjusting for age, fat mass, abdominal adiposity, aerobic power, energy intake, CHO intake and other CVD risk factors ( $r^2 = 0.49$ ,  $p < .01$ ). This suggests that central adiposity and habitual PA are the main predictors of IR in children.

Krekoukia et al. (2007) did not take pubertal stage into account when reporting the influence of habitual PA on HOMA-IR. This is a serious limitation, since the effects of puberty on IR in this 9.5 to 11 yr old population could have affected the results. Seeing that IR increases significantly at the onset of puberty, these findings should be interpreted with caution. Also, the children in their study

wore the accelerometers for 4 days which may not have been long enough to provide a valid estimation of habitual PA. 7 days of monitoring has produced acceptable estimates of daily MVPA in children ( $R = .76$  to  $.86$ ) and has accounted for significant differences in weekday and weekend PA (Trost, 2001). It has only been estimated that 4 days would provide adequate approximations. Lastly, since the time interval, or epoch, in which counts were added, was set at 1 minute, information regarding intensity of activities may have been lost as children often engage in short (just a few seconds), intense bouts of exercise. PA questionnaires could have been used to substantiate the PA data. Questionnaires and interviews can provide valuable information regarding the types of activities children do. This information is important as accelerometers do not record some physical activities (i.e. swimming, bike riding). We suggest that if questionnaires and interviews had been used to substantiate 7 days of PA monitoring, if pubertal stage was taken into account, and if a larger number of subjects were included, PA may have correlated with IR after adiposity was accounted for.

Schmitz et al. (2002) found a significant correlation for fasting insulin ( $r = -0.12$ ,  $p = 0.03$ ) and insulin sensitivity ( $r = 0.13$ ,  $p = 0.001$ ) with PA scores measured by questionnaire in a large sample ( $n=357$ ) of African American and Caucasian 10 to 16 year old children. These associations took age, sex, ethnicity and pubertal stage into account. Consistent with similar studies in adults, further adjustment for body fat percentage and waist circumference did not alter these observations. This is impressive given the fact that adiposity is likely on the causal pathway between activity and IR and adjustment probably removed some of the true association.

Because a subjective method of measuring PA was used in this study, habitual PA could have been over or under-estimated. Schmitz did not compare the strengths of the associations in the ethnic groups.

Brage et al. (2004) found an inverse relationship between objectively measured PA and fasting insulin in a sample of predominantly Caucasian 9 to 10 year old children ( $r = -.23$ ,  $p = .001$ ). They found this association even after adjustment for age, puberty, gender, ethnicity, birth weight, parental smoking, and socioeconomic status. The significant association remained after further adjustment for BMI ( $\beta = -0.179$ ,  $p = .039$ ) and percent body fat ( $p = .049$ ). The dose-response estimate of PA energy expenditure and fasting insulin in Brage et al. (2004) agrees reasonably well with estimates obtained in Schmitz et al. (2002). Both studies found that an approximate increase of 211 kJ in daily energy expenditure from activity (resulting from an increase of about 50 counts per minute in a child weighing 32.4 kg) would correspond to about a 1.0 pmol/L decrease in fasting insulin. The small difference between the 2 studies may be attributed to underestimation of PA by accelerometer count, overestimation by PA questionnaire and/or differences in pubertal stage or body fatness.

Ehtisham et al. (2005) found no ethnic differences in the relationship of insulin sensitivity with adiposity among Caucasian and South Asian adolescents, suggesting that the ethnic differences in insulin sensitivity relate to ethnic differences in adiposity. In contrast, it has been suggested by others (Brage et al., 2004) that the effects of PA on IR may differ according to ethnicity. Brage et al. (2004) suggest that genetic factors could very well modify the relationship between PA and IR in

children supporting the notion that PA may influence IR differently in First Nations versus Caucasian youth.

Ku et al. (2000) investigated the role of both physical fitness and PA in determining IR in a bi-racial sample of pre-pubertal African American and Caucasian children. They found that the volume of PA and the volume of vigorous PA (hours per week determined by questionnaire) were independently related to insulin sensitivity (OGTT) after adjusting for ethnicity and total body fat mass ( $p = .0018$  and  $.0169$ ). It should be noted that diet was not taken into account when interpreting their data.

From their findings and in combination with others, Ku et al. (2000) concluded that racial differences in IR have their origin in childhood and are unlikely to be explained by differences in physical fitness or activity. After all, their African American children were more active yet more IR than their Caucasian counterparts. This suggests that African American children may require more PA than Caucasian children to achieve normal glucose tolerance. No comments were offered regarding the strengths of the associations in the ethnic groups leaving the question about the impact of habitual PA on IR in different ethnic groups unanswered.

Only one study has examined the cross-sectional relationship between PA and IR in a young Aboriginal population. Bunt et al. (2003) found a weak association between PA behaviour (measured by questionnaire) and insulin sensitivity ( $r = .21$ ,  $P = .05$ ), and a moderate association between an objective measure of PA level (the doubly labelled water method) and insulin sensitivity ( $r = .39$ ,  $p = .03$ ) in a group of 10 yr old Pima Indian children. This relationship was not

independent of weight or adiposity. They also found that the children who remained relatively more active between 5 and 10 years of age had smaller decreases in insulin sensitivity, which were partly independent of changes in adiposity. This highlights the importance of establishing an active lifestyle early in life. Indeed, the early establishment of an active lifestyle can improve IR, regardless of the degree of adiposity.

Bunt et al. (2003) suggest that questionnaire variables may be better at recording habitual PA than the doubly-labelled water (DLW) method used in their study. Although the DLW method is the gold standard when it comes to measuring energy expenditure, the authors suggest that it may not capture critical aspects of PA such as type or intensity, which may be important for stimulating the adaptations that lead to improved IR. For instance, the DLW method does not distinguish between weight-bearing and non-weight bearing activity or between exercise and non-exercise activity, such as fidgeting.

In contrast to the studies reviewed, Craig et al. (1996) found a positive relationship between PA and IR in pre-pubertal girls. Their analyses were not adjusted for puberty or adiposity, two strong predictors of IR, likely explaining the equivocal finding.

From these 6 studies of childhood PA and IR, 5 found a significant correlation between PA and a measure of IR. Some gaps in the literature still exist however. Uncertainty regarding the relationship between PA and IR independent of adiposity remains. From the 5 studies reviewed that found a significant relationship, 3 found an association when adiposity was accounted for (Ku et al., 2000; Schmitz et

al., 2002; Brage et al., 2004). Several studies used fasting insulin as an index of insulin sensitivity because it is much easier to measure in children than the gold-standard oral glucose tolerance test (OGTT). It is important to note that fasting insulin underestimates the magnitude of the potential for PA to improve insulin sensitivity, possibly explaining the inconsistent findings in the literature. Less accurate subjective measures of PA may have also contributed to the inconsistencies. Three studies examined this relationship using objective measures of PA. Two studies used the preferred accelerometers to determine habitual PA. Both of these studies limited their examination of this relationship in Caucasian participants.

While the relationship between habitual PA and IR has been examined in Caucasian, African American, and Pima Indian paediatric groups (Bunt et al., 2003; Ku et al., 2000; Schmitz et al., 2002), no study has investigated it in First Nations youth. Furthermore, no study has used accelerometers to examine the relationship in any North American Aboriginal population. Given the high prevalence of physical inactivity and obesity in this vulnerable population, this relationship requires immediate attention.

#### *2.4 Measurement tools*

##### a) Questionnaires

The 22-item Action Schools! BC Food Frequency Questionnaire (AS! BC FFQ) was adopted from the National Institute of Health's (NIH) Eating at America's Table Study, Quick Food Scan. While the full NIH Diet History Questionnaire (DHQ) performed better than similar short food screeners in estimating median

intakes of fruits and vegetables for example (Thompson et al., 2000), the length of the DHQ (i.e. frequency and portion size questions for 65 individual fruits and vegetables) makes it impractical for use in children in a school-based study with time limitations. Thompson et al. (2000) suggest that for studies examining the relationship between fruit and vegetable intake, for example, and some outcome measure, the shorter food screeners and the long DHQ are similar in performance.

When conducted with a random sample population, a single 24-hour recall is appropriate for estimating group means (McPherson et al., 2000). The 24-hour recall has been validated using combined observations from parents and trained personnel ( $r$  for energy consumed = 0.59) (Lytle et al., 1993). Further research has shown modest correlations between observed and 24-hour recall intake of fruit and vegetables in fourth grade children, with the differences suggesting that children are likely to overestimate their consumption of fruit and accurately recall vegetable intake (Lytle et al., 1998). The impact of cognitive limitations and social desirability on the assessment of dietary habits in children and youth should not be ignored in the interpretation of the diet data.

#### b) Physical activity

The DLW method is the gold-standard for determining energy expenditure. It does have limitations however and is very expensive and hard to acquire.

Questionnaire-based assessment of PA, which is the most common subjective method of assessing energy expenditure, can be imprecise, particularly in children. It is recommended that in children 11 yrs or younger, self-report methods are not used as they are unreliable (Brage et al., 2004). Instead, second-generation activity

monitors, such as heart rate monitors, pedometers and accelerometers, are recommended (Brage et al., 2004). Use of these monitors avoid the problems associated with self-report methods and allows for the estimation of PA patterns over time. Advanced data storage capabilities allowing for the assessment of frequency, intensity and duration of PA as well as real-time sampling features which allow for the measurement of PA patterns, make accelerometers the monitors of choice in contemporary PA research, particularly in paediatric populations.

Despite the widespread use of the ActiGraph GT1M accelerometer (Fort Walton Beach, Florida) to assess PA, considerable doubt remains on how to clean and reduce the data as well as how to convert its output into energy expenditure or physical activity intensities. Often, the most appropriate methods for examining and using accelerometer data are hypothesis driven and population specific. Depending on the cohort, the most suitable ways of profiling PA behaviour, of collecting and reducing accelerometer data and of choosing outcome variables may vary. Esliger et al. (2005) suggest best practices for optimizing and standardizing the use of accelerometer data in order to encourage consistency among researchers. Recommendations by Esliger et al. (2005) and procedures developed by the Action Schools! BC PA initiative guided the data cleaning and reduction process in this study (Appendix 4).

*i) Determining moderate- to vigorous-intensity physical activity cut-off values:*

Doubt exists about which regression equation is best at estimating PA intensity in free-living children and adolescents. In a Trost et al. (2006) study comparing three equations (Freedson et al., 2005; Puyau et al. 2002; Trost et al.

1998), it was determined that their ability to differentiate moderate- from light-activity ranged from fair to good, with the weight-specific Trost et al. (1998) equation and the age-specific Freedson et al. (2005) equation exhibiting the highest and second-highest classification accuracies. Trost et al. (2006) suggest that these 2 equations are the most useful for estimating PA intensity in field-based, youth studies.

c) Anthropometry

Establishing an accurate estimate of total body fat is critical when examining the effect of PA on IR. The BMI is viewed as a valid measure of obesity in children and adolescents (Pietrobelli et al., 1998). BMI, while crude, is an easy, fast and non-invasive way of estimating total body fat. Studies suggest that body fat quantity and distribution may differ among ethnic groups and that BMI may overestimate body fatness in First Nations populations because they tend to have a higher proportion of fat-free mass (Lohman et al., 2000). It has also been shown that First Nations people have a greater proportion of abdominal or intra-abdominal fat compared to Caucasians (Potvin et al., 1999/8; Lohman et al., 2000; Young et al., 2000). Finally, estimates of body fat based on BMI reference data ( $\geq 85^{\text{th}}$  percentile) may underestimate obesity in First Nations populations (Potvin et al., 1999/8; Lohman et al., 2000; Young et al., 2000). For these reasons, BMI is generally considered to be only a rough estimate of total body fat.

Given all the limitations inherent in using the BMI to estimate body fat, it was the most appropriate method available in the current study. As far as defining body fat from BMI, Cole et al.'s international BMI cut-offs are the most appropriate

for determining overweight and obesity in First Nations youth. The main reason being that they are based on a heterogeneous mix of large nationally representative surveys with varying prevalence rates of obesity (Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States) rather than on U.S. data exclusively (i.e. Center for Disease Control cut-offs).

### *Summary*

The relationship between objectively measured PA and IR in First Nations youth warrants special attention. Relevant studies have examined this relationship in Caucasian and some ethnic populations and have produced valuable findings. Despite the urgency of the D2 problem in First Nations populations a lack of research has left gaps in the knowledge of behavioural factors affecting the disease.

In addition to examining the relationship in a new cohort, the present study overcame some of the limitations identified in the studies reviewed. Namely the present study used a 15 second epoch in measuring habitual PA. Using a 15 second epoch allows researchers to better assess intensity and duration of activity. The present study also took maturity, BMI, central adiposity, CRF and diet into account when examining the relationship in question as each of these have been shown to influence IR. Finally, the strengths and weaknesses of the measurements in the current study have been outlined and considered in the interpretation of the results.

## Chapter 3: Methodology

Chapter three is divided into five sections: experimental design, participants, testing schedule, measurements, and statistical analysis. Fasting blood samples were collected in September 2006 and May 2007 in 2 First Nations communities in northern BC, Hartley Bay and Kitkatla. The remainder of the data collection occurred between September 10<sup>th</sup> and 21<sup>st</sup> 2007 in these same two communities. The University of British Columbia and the University of Victoria Human Ethics Research committees provided approval for this study to be conducted.

### *3.1 Experimental Design*

The present study investigated the cross-sectional association between accelerometer-derived habitual PA (counts/min, MVPA/day, sedentary activity/day) and indices of IR (HOMA-IR, fasting insulin) in a paediatric First Nations population.

### *3.2 Participants*

#### a) Special considerations for subject recruitment

Special considerations were taken in the design and delivery of this research project. There are historical reasons why First Nations people may legitimately feel apprehensive about the activities of researchers.

The current project reflects the priorities of both the First Nations community and the research group, in accordance with principles, practices and procedures for conducting health research in a First Nations context. The guidelines for conducting

health research in a First Nations context are outlined by the Canadian Institutes of Health Research (CIHR) (2007) and informed all the phases of the research project. The CIHR (2007) guidelines do not replace ethical standards for the conduct of research on individuals outlined in 'Protocols and Principles for Conducting Research in an Indigenous Context' developed by the Faculty of Human and Social Development at the University of Victoria. Instead, they suggest additional requirements to ensure that the rights and interests of the community as a whole are respected.

b) Recruitment, sample size and inclusion criteria

Dr. C. Panagiotopoulos (University of British Columbia, Department of Paediatrics), invited First Nations guardians and their children living in 2 northern BC First Nations communities, Hartley Bay and Kitkatla, to participate in the study. The protocol was explained to the guardians and children and signed informed consent was obtained from one guardian. 74 First Nations youth from Hartley Bay and Kitkatla volunteered to participate in the study.

Volunteers with a chronic disease or condition inhibiting participation in physical activities (i.e. Down's syndrome, Cushing's syndrome, or other physical or mental disabilities or injuries) were excluded from the study. Volunteers with resting blood pressure measurements greater than 160/100 did not participate in the aerobic test and thus were excluded from the analysis.

Participants with a full data set, including anthropometric, diet, physical activity (PA), insulin resistance (IR) and pubertal status data were included in the

study. Participants were excluded from the statistical analysis if they had any missing data.

### *3.3 Procedures*

This study involved 3 data collection periods. Fasting blood samples were collected in Hartley Bay and in Kitkatla in September 2006 and May 2007 respectively. The rest of the data collection, including anthropometrics, PA, cardio-respiratory fitness (CRF) assessment, and dietary analysis occurred in September 2007 at both sites. The methodological information detailed in this thesis is of that employed for the data collection in September 2007 and the subsequent analysis.

All testing was conducted at the local village school during regular school hours by members of the research team. All participants signed child assent forms to confirm that their involvement in the study was voluntary and that they could withdraw from participation at any time without penalty and loss of benefit to themselves.

#### a) September 2007: Morning Testing

The first part of the testing day included fitting the participants with ActiGraph GT1M accelerometers and distributing the physical activity logs. Next, anthropometric measures, including height, weight, and waist and hip circumferences, resting blood pressure, and 3 questionnaires were administered. Table 1 provides a timeline for a morning testing schedule. This timeline allowed 5 members of the research team to assess 6 children in approximately 36 minutes.

**Table 1.** Morning data collection schedule, including anthropometry, and the 24-hr food recall (FRQ), food frequency (FFQ) and physical activity (PAQ) questionnaires.

<b>Time (min)</b>	<b>Anthropometry</b>	<b>24-hr FRQ (station 1)</b>	<b>24-hr FRQ (station 1)</b>	<b>FFQ and 7-day PAQ</b>
<b>0-6</b>	Child 1	Child 2	Child 3	4, 5, 6
<b>6-12</b>	Child 4	Child 2	Child 3	1, 5, 6
<b>12-18</b>	Child 2	Child 5	Child 4	1, 3, 6
<b>18-24</b>	Child 6	Child 5	Child 4	1, 2, 3
<b>24-30</b>	Child 5	Child 1	Child 6	2, 3, 4
<b>30-36</b>	Child 3	Child 1	Child 6	2, 4, 5

b) September 2007: Afternoon Testing

In the afternoon of the test day, each participant completed the 20 meter Leger-Boucher aerobic shuttle run to exhaustion (Leger et al., 1988). Participants performed the shuttle run in class groups, with no more than 10 participants at a time.

c) September 2007: Accelerometers returned

The accelerometers and activity logs were collected at the schools 5 to 7 days after they were originally distributed, depending on the community. The return rate was high with only one accelerometer lost.

*3.4 Measurements*

a) Anthropometry

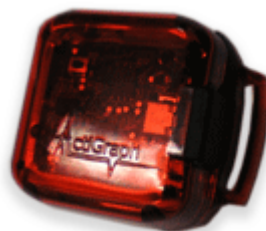
All anthropometric measurements followed Canadian Society of Exercise Physiology (CSEP) protocol and were taken by a physician. An electronic digital scale (Conair digital electronic scale) was used to weigh participants to the nearest 0.1 kg. Weight was taken with shoes removed. Stretched standing height was measured to the nearest 0.1 cm using a portable stadiometer (Seca 214 Portable Stadiometer). Measurements were taken as per CSEP protocol.

Body mass index (BMI) was calculated from weight and height according the formula,  $\text{weight (kg)} / \text{height}^2 \text{ (m)}$ . Cole et al.'s (2000) international age- and gender-specific BMI cut-offs for overweight and obesity were used (Appendix 1). These cut-offs are the most appropriate for determining overweight and obesity in First Nations youth and were used in the 2002/03 First Nations Regional Longitudinal Health Survey (RHS 02/03), the most comprehensive First Nations health survey in Canada (First Nations Information Governance Committee, 2005). BMI does not account for variations in fat distribution or body composition and thus is a relatively crude measure of adiposity. This is especially true in First Nations people who have a greater proportion of fat-free mass and more abdominal fat as a proportion of total

fat than previously studied populations (Lohman et al., 2000). Since BMI alone is a rough estimation of body fat and since it may have less predictive validity in First Nations populations, three measures of central obesity, including waist circumference (minimal girth of the abdomen - measured 1 cm above the top of the iliac crest), hip circumference (widest part of the hip) and waist to hip ratio were also included in the analysis to help define adiposity in this cohort. Waist and hip circumferences were measured to the nearest 0.1 cm using CSEP protocol. BMI z-scores (zBMI) were calculated from the age- (year and month) and gender-specific growth references for school-aged children and adolescents developed by the World Health Organization (Onis et al., 2007).

b) Physical activity

Physical activity was assessed using the ActiGraph GT1M uniaxial accelerometer (LCC, Fort Walton Beach, FL, USA) designed to measure and record accelerations in the vertical plane. The ActiGraph is a small (3.8 x 3.7 x 1.8 cm) and lightweight (27 g) instrument which is initialized and downloaded using ActiLife Lifestyle Monitor Software (v.3.2.8) and has no external controls that can be manipulated.



**Figure 8.** ActiGraph GT1M uniaxial accelerometer (LCC, Fort Walton Beach, FL, USA).

Prior to distributing the accelerometers, reliability testing was performed to ensure that intra- and inter-accelerometer variability was within acceptable ranges. One ActiGraph failed to record data during the testing and thus was not used in the study. The rest of the ActiGraphs recorded similar outputs at varying treadmill speeds (i.e. slow walk, brisk walk, slow run, fast run).

The accelerometers were programmed to record data, or ‘counts’, every 15 seconds. Data are expressed as average PA intensity, or total counts per registered time ( $\text{counts} \cdot \text{min}^{-1}$ ), average time spent in MVPA ( $\text{min} \cdot \text{day}^{-1}$ ) and average time spent in sedentary activities ( $\text{min} \cdot \text{day}^{-1}$ ), to produce measures of habitual PA.

The Freedson et al. (2005) age-specific regression equation was used to convert ActiGraph counts into units of energy expenditure (metabolic equivalent or METs) corresponding to MVPA thresholds:

$$\text{METs} = 2.757 + (0.0015 \times \text{counts per minute}) - (0.08957 \times \text{age (yr)}) - (.000038 \times \text{counts per minute} \times \text{age (yr)})$$

(Freedson et al., 2005)

MVPA was defined as intensities  $\geq 3$  METs consistent with that commonly used by others (Freedson et al., 2005). Sedentary activity was defined as  $\leq 50 \text{ counts} \cdot \text{min}^{-1}$ .

The participants wore the accelerometers snugly over the right hip as per ActiGraph directions for all waking hours, except during water-based activities. Students with data for at least 3 monitored days were included in the study.

The concern that participants artificially increase their activity because they are wearing an activity device and are being ‘observed’ is referred to as ‘subject reactivity’. Esliger et al. (2005) did not observe amplified activity counts at the start of data collection (with a delayed start time) in three different samples. In the present study monitors were distributed the day before the start of data collection, delaying start time, in an attempt to reduce subject reactivity and allow the same start time for all the participants regardless of what time of day they received their monitors.

Each child was given a physical activity log in which they were instructed to record the time they spent wearing the accelerometer (Appendix 5). The logs were used to place the accelerometer data into context and also served to remind children to wear the accelerometers and thus increase compliance. To provide incentive for wearing the accelerometer, participants who returned the accelerometers and the completed physical activity logs at the end of the week were entered into a draw to win a special prize.

Often, the most appropriate methods for examining and using accelerometer data are hypothesis driven and population specific (Esliger et al., 2005). Depending on the cohort, the most suitable ways of profiling PA behaviour, of collecting and reducing accelerometer data and of choosing outcome variables may vary. The current study adhered to previously defined data reduction protocols (Esliger et al., 2005) and utilized certain population specific procedures to ensure a consistent yet culturally-appropriate approach to the data. For example, since the vast majority of the participants in this study recorded numerous bouts of zero counts greater than 10 min each day, and given the population’s generally sedentary lifestyle, it was

concluded that the monitors were not likely being taken off and put back on several times each day. As a result, it was decided to interpret only strings of zero counts greater than the average longest motionless bout for similarly aged children (approximately 60 minutes) as ‘time not worn’, as opposed to the ‘10 minute rule’ utilized in other studies. By reducing the data in this way we avoided excluding true bouts of motionless data. For more detail on the data cleaning and reduction procedures employed in this study refer to Appendix 4.

c) Cardio-respiratory fitness

The Leger-Boucher 20 meter shuttle run, a maximal aerobic running test, was used to assess cardio-respiratory fitness (CRF). The participants wore running shoes and gym or street clothes during the test. They were verbally encouraged throughout the test. The test was conducted in the village school gymnasiums. Completed stages were recorded by members of the research team. Maximal oxygen consumption was predicted ( $VO_{2max_{pred}}$ ) from the maximal aerobic shuttle running speed ( $X_1$ ,  $km \cdot h^{-1}$ ) and age ( $X_2$ ):

$$VO_{2max_{pred}} = 31.025 + 3.238X_1 - 3.248X_2 + .1536X_1X_2$$

(Leger et al., 1988)

d) Blood parameters

Baseline venous blood samples were obtained after an overnight fast for measurement of fasting plasma glucose and insulin. The samples were taken in the morning at the village health center. The blood was spun, aliquoted, and stored in a -20°C freezer. Blood from the venipuncture was immediately analysed at the point-of-

care for glucose levels (Ascensia Contour(R) glucometer, Bayer Inc., Toronto, Canada). At the completion of the week of screening, frozen samples were transported by float plane to BC Children's Hospital in Vancouver for analysis. Insulin was analyzed using the Access Immunoassay Systems Ultrasensitive Insulin Ref 33410.

*i) HOMA-IR*

IR was estimated from fasting insulin ( $\mu\text{U/ml}$ ) and fasting glucose ( $\text{mmol/L}$ ) using the homeostasis model assessment estimate of IR (HOMA-IR). HOMA-IR was calculated employing the equation of Matthews et al. (1985) as follows:

$$\text{HOMA-IR} = [\text{G}_F \times \text{I}_F] / 22.5$$

(Matthews et al., 1985)

HOMA-IR has been validated against the gold standard for investigating and quantifying IR, the euglycemic-hyperinsulinemic clamp ( $\text{IS}_{\text{EU}}$ ) ( $r=-0.57$ ). The  $\text{IS}_{\text{EU}}$  measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycaemia. HOMA-IR has excellent and comparable correlations with the  $\text{IS}_{\text{EU}}$  in pre-pubertal and pubertal, and non-obese and obese African American and Caucasian children (Gungor, Saad, Janosky & Arslanian, 2004; Yeckel et al., 2004). HOMA-IR also reflects differences in IR between pre-pubertal and pubertal children, and non-obese versus obese children (Gungor et al., 2004). An important limitation though, is that it is calculated from baseline measurements of glucose and insulin, whereas the IR associated with obesity and physical inactivity is mainly the result of the inability of increased insulin concentrations to enhance peripheral glucose uptake.

*ii) Impaired fasting glucose*

Impaired fasting glucose (IFG) represents the range of fasting plasma glucose between 'normal' and diabetic. In the present study, IFG was defined as fasting plasma glucose concentrations between 5.6 and 6.9 mmol/L which is consistent with recent modifications to standards (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). The threshold separating diabetes from non-diabetes is 7.0 mmol/L.

Several different thresholds for HOMA-IR have been used in pediatric studies, ranging from 2.10 to 3.16. Tresaco et al. (2005) determined that 2.28 did the best job of discriminating between the absence or presence of the metabolic syndrome in a sample of obese and non-obese pre-pubertal and pubertal boys and girls (n=140; 11.02 ± 2.11 yrs; range=7-16; 41 M, 33 F). The present study reports the prevalence of IR using the Tresaco et al. (2005) HOMA-IR threshold.

*iii) Pubertal status*

Pubertal status (pre- vs. pubertal) was assessed using serum estradiol levels in girls and serum total testosterone levels in boys (Fisher, 1998). Girls were classified as pre-pubertal if their serum estradiol concentration was less than 60 pmol/L (Tanner Stage 1 upper limit is 36.7 pmol/L) (Fisher et al., 1998). Boys were classified as pre-pubertal if their serum total testosterone concentrations were below the upper limit of the Tanner Stage 2 range (2.4 nmol/L) provided by Fisher et al. (1998).

All other participants with androgen levels above these cut-off values were classified as pubertal. Estradiol, the principal estrogenic hormone, in serum was

analyzed using the Pantex Estradiol (E2)<sup>125</sup> I kit (catalogue no. 047) (Santa Monica, CA). Serum total testosterone was measured using the DSL-4100 Testosterone Radioimmunoassay (RIA) kit (Webster, Texas).

e) Questionnaires

*i) Demographic*

Demographic information including name, grade, sex and date of birth were collected in the same session as the anthropometric measurements.

*ii) Diet*

Dietary intake was assessed using the Action Schools! BC (AS! BC) Food Frequency Questionnaire (FFQ) (Appendix 6) and the AS! BC 24-Hour Food Recall Questionnaire (24-FRQ) (Appendix 7). Both questionnaires were adapted for the purpose of this study. The FFQ is a 22-item questionnaire adopted from the National Institute of Health's (NIH) Eating at America's Table Study, Quick Food Scan. Trained interviewers helped participants fill out the questionnaires. There were two FFQ trained interviewers per six participants. Data from the FFQ were organized into summary variables (i.e. sugar-sweetened beverage was created from the sum of 100% fruit juice, regular soft drink and other high sugar liquids).

The 24-FRQ was a face-to-face interview in which a researcher asked the participant to list everything he or she ate or drank, including ingredients and portion sizes, during the previous day. Prompts or food models for accurate recalls of portion sizes, such as plates, bowls, measuring cups and common food containers were used to cue memory.

The data from the 24-FRQ were analyzed using ESHA's 'The Food Processor' Nutrition and Fitness Software (v.8.7). Estimates of total energy intake (kcal/day) and servings (U.S.) of fruits and vegetables, as well as grams of carbohydrates, sugar and dietary fibre consumed were calculated. These variables were chosen because they are known to influence fasting insulin and glucose levels, as well as IR (Reaven, 2005).

All completed questionnaires were reviewed and initialled by 2 members of the research team for quality control. If mistakes were found, members of the research team reviewed the answers with the participants.

f) Blood Pressure

Blood pressure was measured with the participant seated quietly after a 5 minute rest using an automated sphygmomanometer (Critikon Dinamap Vital Signs Monitor 1846 SX). It was measured three times and the average was taken of the second two measurements. Appropriate cuff size was used for each subject to increase measurement accuracy.

*3.5 Limitations of the research design and methods*

1) Cross-sectional design: Three to six days of PA monitoring represents only a fraction of the time that may be important for influencing IR.

2) Staggered data collection: Habitual PA, anthropometry, diet and CRF were measured approximately 4 and 12 months after IR was assessed. Changes in habitual PA, anthropometry and diet over this period (i.e. due to maturational or seasonal differences in PA and diet) were not considered.

3) Issues in accelerometry:

a) Cycling, swimming and weight bearing activities were not captured.

b) Freedson et al.'s (2005) age-predicted regression equation was used to determine MVPA thresholds from accelerometer 'counts'. Equations incorporating weight may have provided more accurate MVPA thresholds and thus better estimates of MVPA. Until further research is conducted to identify procedures for adjusting for age and weight however, it has been recommended that age-specific equations be used (Esliger et al., 2005).

c) Four days of monitoring have shown to provide reliable estimates of habitual PA (Esliger et al., 2005). Three or more days of objective PA monitoring were used in this study however and may not have provided reliable estimates of daily PA behaviour in the participants. Stringent criteria for a valid day, the fact that other studies have used the 3 day inclusion criteria (Brage et al., 2004) and that the majority of the participants in the study (64%) recorded at least 4 monitored days, including at least 1 weekend day, suggest that the inclusion criteria utilized were appropriate.

d) Compared to other studies (Krekoukia et al., 2007; Anderson et al., 2006), the amount of time spent in MVPA may be 'inflated' in this study because the accelerometers were programmed to record data, or 'counts', every 15 seconds (as opposed to 60 seconds). Conversely, including bouts of motionless data of up to approximately 60 minutes may have diluted our measure of average PA intensity.

4) Determining dietary habits: The 24-FRQ's were administered on Tuesday, Wednesday and Thursday in Kitkatla thus recording food consumed on a weekday.

In Hartley Bay, the 24-FRQ's were administered on a Monday, thus recording food consumed on Sunday, a weekend day. Since diet is believed to vary depending on the day of the week (i.e. weekday versus weekend day) information regarding dietary habits should be interpreted with caution.

5) Indirect measurements of insulin resistance, total adiposity and cardio-respiratory fitness: The gold standard for assessing IR is the hyperinsulinemic-euglycemic (IS<sub>EU</sub>) clamp. It is labor intensive, costly and relatively invasive and was not suitable for use in this study. Given all the limitations inherent in using the BMI to estimate total body fat, it was the most appropriate method available. The Leger-Boucher 20 m shuttle run to exhaustion provides reliable estimates of maximal oxygen uptake in children ( $r=.89$ ) and was the most suitable method for predicting CRF in this study.

6) Determining pubertal status: All the participants with androgen concentrations above the cut-offs, including participants who may have been post-pubertal, were classified as 'pubertal' in the analysis. Misclassifying sexually mature participants as pubertal may have altered our findings.

### *3.6 Statistical analysis*

Data from diet questionnaires and from the accelerometers were recorded and stored in a password protected university computer and analyzed using specially designed software. The same researcher cleaned and reduced all the files ensuring a consistent approach to the analysis. Data from one accelerometer were discarded due to a technical malfunction. Data from the fasting blood samples, anthropometrics,

CRF, and accelerometers, as well as information from the diet questionnaires were statistically analyzed using the SPSS software (v. 16.0, SPSS, Chicago, IL).

Only participants with complete data sets (the complete group) were included in the analyses (n=39). Analyses were conducted for the complete group, as well as when the complete group was stratified into subgroups: gender (boys, girls), pubertal status (pre-pubertal, pubertal), weight status (non-overweight, overweight or obese) and physical activity (low, high physical activity) subgroups (Table 2). Participants who were above the mean for MVPA were classified in the high physical activity (HPA) subgroup, and those who were below the mean were classified in the low physical activity (LPA) subgroup.

**Table 2.** Participants with complete data sets (n=39) were stratified by gender, pubertal status, weight status and physical activity level for subgroup analyses.

<i>Subgroups</i>
1. Gender
<i>Male</i> (n=16)
<i>Female</i> (n=23)
2. Pubertal Status
<i>Pre-</i> (n=24)
<i>Pubertal</i> (n=15)
3. Weight Status
<i>Non-overweight</i> (n=20)
<i>Overweight or obese</i> (n=19)
4. Physical activity
<i>High-</i> (n=20)
<i>Low-</i> (n=19)

Asymmetrical distribution was defined as variables with kurtosis and skewness values greater than  $\pm 2$ . Asymmetric variables were not transformed when examining differences in means between subgroups; however, they were

transformed, as necessary, for use in the correlation and regression analyses in order to enable accurate comparisons with similar studies. Significant alpha was set at 0.05 and the analyses tested null hypotheses.

a) Tests for differences in means

Independent samples t-tests were used to examine differences between means of the groups with complete (n=39) and incomplete (n=35) data sets on all the independent predictors, including anthropometric, PA, diet and IR variables. T-tests were also used to test for differences in IR between gender, puberty, weight status and PA subgroups.

b) ANCOVA for differences in means

Analyses of covariance (ANCOVA) were used to control for the effect of age on anthropometric, PA, CRF and diet variables, as age is known to influence these predictors. As pubertal status is known to affect IR, it was also a covariate when examining the differences in IR between gender, weight status and PA subgroups.

c) Correlation analyses for predictors of IR and indices of IR

Partial correlation coefficients (r) were used to evaluate the age- and puberty-adjusted associations between predictors of IR (anthropometric, PA, CRF and diet variables) and indices of IR (HOMA-IR, fasting insulin) in the complete group as well as in the subgroups. Further analyses were conducted adjusting for zBMI and waist circumference separately. The correlation analyses were two-tailed.

d) Multiple regression analysis predicting IR

A stepwise multiple linear regression analysis was used to determine the best predictors of HOMA-IR in the current sample of First Nations youth. Age, sex,

pubertal status, average PA intensity ( $\text{counts}\cdot\text{min}^{-1}$ ), MVPA ( $\text{min}\cdot\text{day}^{-1}$ ), sedentary activity ( $\text{min}\cdot\text{day}^{-1}$ ), diet variables, CRF, zBMI, and measures of central obesity were included in the regression.

Standardized regression coefficients ( $\beta$ ) were also calculated. This coefficient was obtained when variables were converted (separately) to z-scores. Standardized coefficients were necessary in order to compare the PA regression coefficient in the present study to those in similar studies with Caucasian participants.

The correlation and regression analyses were used to determine the association between the activity exposure (PA) and the outcome (IR) in our sample, and whether confounding factors can be ruled out as an alternative explanation for the association.

## Chapter 4: Results

### *4.1 Participant characteristics*

Only the 39 participants of the original 74 had complete data sets (subjects with all anthropometric, physical activity (PA), diet, pubertal status and insulin resistance (IR) data) will be discussed in this study. 35 initial participants were excluded from the data analysis because they had missing data. Of those, 20 did not have valid accelerometer data, with fewer than 3 monitored days, and 15 were absent when fasting blood samples were collected.

Mean BMI and zBMI, waist circumference, dietary habits, average PA intensity, moderate to vigorous intensity physical activity (MVPA), and cardio-respiratory fitness (CRF) of the 39 participants with full data sets did not differ from the means of the group with incomplete data sets (n=35). This provides evidence of the representativeness of the ‘complete’ group to the larger remote, rural youth community. Table A1 (Appendix 8) illustrates the characteristics of participants with complete (n=39) and incomplete data sets (n=35).

The remainder of this section refers only to the 39 participants with complete data sets. The physical characteristics of the participants with complete data sets, separated by gender, are shown in Table 3. Within this group, 49% were overweight or obese as defined by internationally accepted age- and sex-specific cut-offs (Cole et al., 2000) (Appendix 1). 64% of the participants wore the accelerometer on at least 4 days (at least 3 weekdays plus at least 1 weekend day) for an average of  $12.7 \pm 1.32$  hours $\cdot$ day $^{-1}$ . The average time spent in MVPA was  $139.34 \pm 34.36$  minutes $\cdot$ day $^{-1}$ .

**Table 3.** Unadjusted mean ( $\pm$ sd) age, pubertal status and anthropometric characteristics of First Nations boys and girls.

<i>Variable</i>	<i>Boys (n=16)</i>	<i>Girls (n=23)</i>
Age (y)	12.3 $\pm$ 1.9	11.4 $\pm$ 2.4
Pubertal status $\blacklozenge$ (pre-pubertal/pubertal)	11/5	13/10
Weight (kg)	52.69 $\pm$ 17.85	49.80 $\pm$ 16.47
Height (m)	1.53 $\pm$ 0.14*	1.46 $\pm$ 0.10
BMI (kg·m <sup>-2</sup> )	21.89 $\pm$ 4.80	22.80 $\pm$ 4.83
zBMI	1.18 $\pm$ 1.23	1.49 $\pm$ 0.95
Waist circumference (cm)	74.86 $\pm$ 14.39	71.77 $\pm$ 11.43
Hip circumference (cm)	84.43 $\pm$ 12.31	86.54 $\pm$ 13.08
Waist:Hip	0.88 $\pm$ 0.07	0.83 $\pm$ 0.05
Overweight or Obese (%)	31.25	60.87

$\blacklozenge$ Data are ratios; \*p<.05 for difference between boys and girls.

#### 4.2 Prevalence of insulin resistance and impaired fasting glucose

Mean fasting glucose, fasting insulin and HOMA-IR values are provided in

Table 4.

**Table 4.** Unadjusted mean ( $\pm$ sd) fasting glucose, fasting insulin and HOMA-IR (n=39).

<i>Fasting Plasma Glucose</i> (mmol·L <sup>-1</sup> )	<i>Fasting Plasma Insulin</i> (pmol·L <sup>-1</sup> )	<i>HOMA-IR</i>
5.22 $\pm$ 0.38	52.15 $\pm$ 35.27	1.79 $\pm$ 1.25

The proportion of participants with impaired fasting glucose (IFG) was 18% (fasting glucose  $\geq$  5.6 and  $<$  7 mmol·L<sup>-1</sup>), while the prevalence of IR was 25.6% (HOMA-IR  $\geq$  2.28). No participants were diabetic (i.e. fasting glucose concentration  $\geq$  7 mmol·L<sup>-1</sup>). Table 5 shows the frequency and prevalence of IFG and IR for the complete group as well as for the subgroups. Notably, 85.7% of the participants with IFG (6 out of 7) were classified in the low physical activity (LPA) subgroup. Also,

80% of the participants demonstrating measurable IR (8 out of 10) were overweight or obese. There was no gender difference in IR, although a greater proportion of males exhibited IFG than females. The prevalence of IR, hyperinsulinemia and IFG using different thresholds for HOMA-IR, fasting insulin and fasting glucose are illustrated in Table A2 (Appendix 9).

**Table 5.** Frequency and prevalence (%) of impaired fasting glucose and HOMA-IR in First Nations youth.

<i>Subgroups</i>	<i>Fasting Glucose</i> $\geq 5.6 \text{ mmol}\cdot\text{L}^{-1}$	<i>HOMA-IR</i> $\geq 2.28$
All (n=39)	7 (17.9%)	10 (25.6%)
Pubertal Status		
<i>Pre-</i> (n=24)	5 (20.8%)	3 (12.5%)
<i>Pubertal</i> (n=15)	2 (13.3%)	7 (46.6%)
Gender		
<i>Male</i> (n=16)	5 (31.3%)	4 (25%)
<i>Female</i> (n=23)	2 (8.7%)	6 (26.1%)
Weight Status		
<i>Non-overweight</i> (n=20)	3 (15%)	2 (10%)
<i>Overweight or obese</i> (n=19)	4 (21.1%)	8 (42.1%)
Physical activity		
<i>High-</i> (n=20)	1 (5%)	4 (20%)
<i>Low-</i> (n=19)	6 (31.6%)	6 (31.6%)

#### 4.3 Differences among the subgroups

##### a) Anthropometrics

When taking the effect of age on anthropometric variables into account, pre-pubertal children weighed less ( $p=.048$ ) and had smaller waist circumferences ( $p=.043$ ) than pubertal adolescents, participants in the LPA subgroup were heavier ( $p=.043$ ) than those in the HPA subgroup, and participants classified as overweight or obese had larger waist ( $p=.001$ ) and hip circumferences ( $p<.001$ ) than their non-

overweight counterparts. The differences between boys and girls and between non-overweight and overweight/obese participants changed with age.

b) Physical activity and cardio-respiratory fitness

When the effect of age on PA and cardio-respiratory fitness (CRF) was controlled for, boys accumulated more activity counts·min<sup>-1</sup> (p=.003) and MVPA min·day<sup>-1</sup> (p=.008) than girls. Boys also performed better aerobically than the girls (p=.008). Shuttle run stage, rather than predicted VO<sub>2</sub>max, was used to identify differences in CRF in an attempt to avoid accounting for age twice. The HPA group performed better than the LPA group on the aerobic test (p=.003). Neither pubertal status nor weight status influenced these findings (p>.05).

c) Diet variables

Mean dietary intakes separated by gender are provided in Table 6. Taking into account the influence of age on dietary habits, boys consumed fewer fruits and vegetables (p=.027) and twice as much sugar sweetened beverage (SSB) (p=.038) than the girls. While absolute caloric intake was higher in the boys, once age was taken into account, the boys were found to have consumed approximately 300 fewer kcals·day<sup>-1</sup> than girls (p=.008). The non-overweight group consumed more fruits and vegetables than the overweight or obese group (p=.003). These differences varied with age.

**Table 6.** Unadjusted mean ( $\pm$ sd) dietary intake in First Nations boys and girls.

<i>Diet Variables</i>	<i>Boys (n=16)</i>	<i>Girls (n=23)</i>
Energy intake (kcal·d <sup>-1</sup> )	2243.9±918.6*	1607.8±554.7
Carbohydrate (grams·d <sup>-1</sup> )	360.5±195.7	248.8±82.0
% energy from CHO	63±14	63±12
Sugar (grams·d <sup>-1</sup> )	156.0±124.6	113.4±70.1
Sugar sweetened beverage (mL·wk <sup>-1</sup> )	3620.2±402.07*	1609.0±992.3
Dietary Fibre (grams·d <sup>-1</sup> )	12.1±6.4	13.6±10.1
Fruit & Vegetable (serv·d <sup>-1</sup> )	1.1±1.8*	1.8±1.4
Fruit & Vegetable (serv·wk <sup>-1</sup> )	12.6±7.9	13.1±6.0

\*p<.05 for difference between boys and girls.

#### d) Insulin Resistance

Tests for differences in the unadjusted means of indices of IR among subgroups indicated that the pre-pubertal, the non-overweight/non-obese, and the HPA subgroups had lower fasting insulin (p=.009, .031, .028, respectively) and HOMA-IR (p=.012, .048, .033, respectively) values than the pubertal, the overweight and obese, and the LPA subgroups. When adjusted for pubertal status, the differences between the weight status subgroups were attenuated (p>.05) and the LPA subgroup had higher fasting glucose values than the HPA subgroup (p=.026) with 31.6% of the LPA subgroup and 5% of the HPA subgroup having fasting glucose values greater than 5.6 mmol·L<sup>-1</sup>. No differences were seen between gender groups, before or after adjustment for pubertal status (Table 7).

**Table 7.** Unadjusted mean values ( $\pm$ sd) for indices of insulin resistance in First Nations boys and girls.

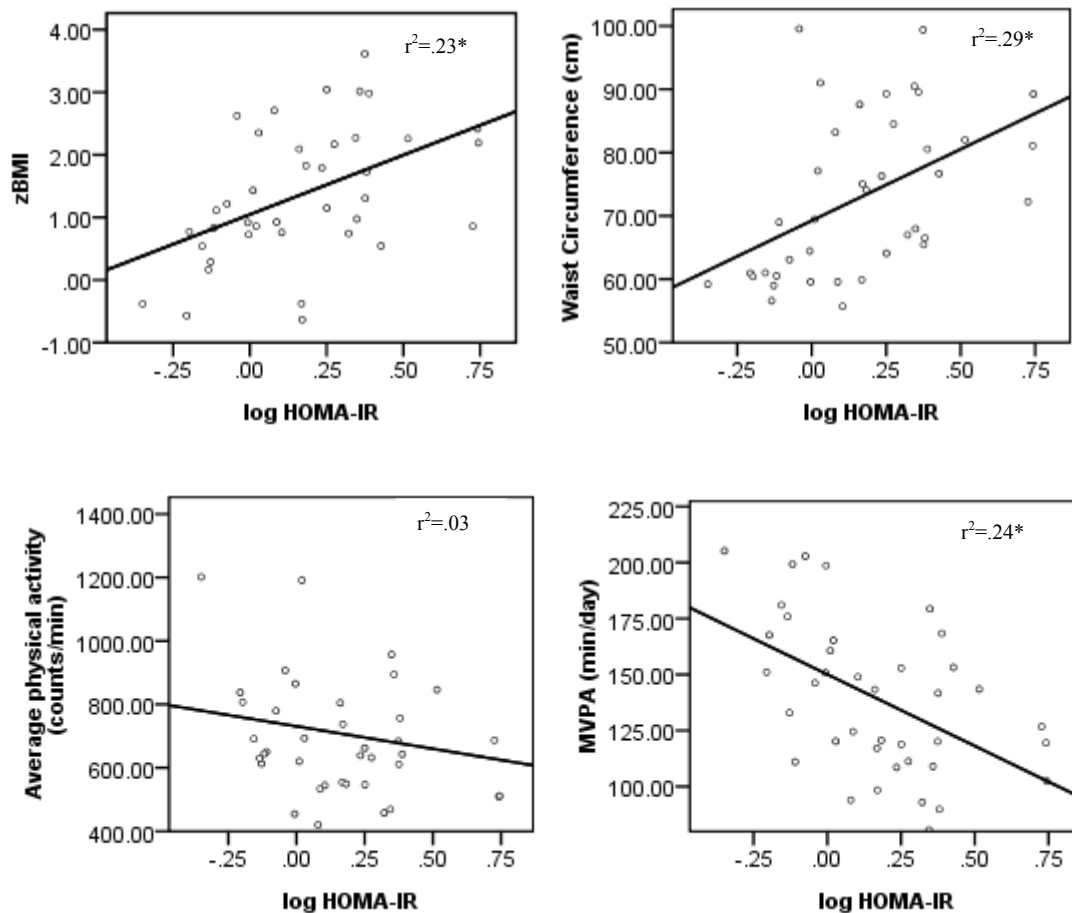
<i>Indices of IR</i>	<i>Boys (n=16)</i>	<i>Girls (n=23)</i>
Fasting glucose ( $\text{mmol}\cdot\text{L}^{-1}$ )	5.26 $\pm$ .48	5.20 $\pm$ .29
Fasting insulin ( $\text{pmol}\cdot\text{L}^{-1}$ )	47.75 $\pm$ 30.70	55.22 $\pm$ 38.49
HOMA-IR	1.67 $\pm$ 1.2	1.88 $\pm$ 1.34

Differences between the subgroups on HOMA-IR predictor variables are shown in Table A3 (Appendix 10).

#### *4.4 Correlation analyses for predictors of insulin resistance with indices of insulin resistance*

##### a) Associations between potential predictors of insulin resistance and indices of insulin resistance

The scatter plots in Figure 9 illustrate the direct relationships between total and central adiposity and HOMA-IR. IR increases concomitantly with zBMI and waist circumference. On the contrary, MVPA was inversely related with HOMA-IR, indicating that as MVPA increases IR decreases.



**Figure 9.** Scatter plots with best fit lines illustrating the unadjusted associations of zBMI, waist circumference, average PA intensity and MVPA (y-axis), against log HOMA-IR (x-axis). \* $p < .05$

Pearson correlation coefficients between indices of IR and anthropometric, PA, CRF and diet variables, adjusted for both age and pubertal status, are presented in Table 8. Several variables were significantly correlated with HOMA-IR and fasting insulin, including zBMI ( $r = .441, .455, p < .01$ ), waist circumference ( $r = .345, .357, p < .05$ ), MVPA ( $r = .449, -.423, p < .01$ ), and predicted  $VO_2\max$  ( $r = -.358, -.358, p < .05$ ).

The relationship between PA and IR was examined after removing the affect of adiposity on IR in order to determine whether PA influences IR independent of its

effect on adiposity, as adiposity is known to have the most significant impact on fasting insulin levels and IR of all the risk factors for D2 (McMurray et al., 2000). Following correction for zBMI, the association between MVPA and HOMA-IR persisted ( $r = -.36$ ,  $p < .05$ ) and no variables were correlated with fasting insulin ( $p > .05$ ). After correcting for waist circumference, MVPA was significantly associated with HOMA-IR and fasting insulin ( $r = -.380$  and  $-.349$ ,  $p < .05$ ).

**Table 8.** Pearson correlation coefficients, adjusted for age and pubertal status, for indices of IR and zBMI, central adiposity, physical activity, diet and cardio-respiratory fitness variables in school-aged First Nations youth ( $n = 39$ ).

	HOMA-IR <sup>b</sup>	FI <sup>b</sup>
zBMI	.441**	.455**
Waist Circumference (cm)	.345*	.357*
Hip Circumference (cm)	.299	.300
Average physical activity intensity (counts·min <sup>-1</sup> )	-.305	-.287
MVPA (min·d <sup>-1</sup> )	-.449**	-.423**
VO <sub>2</sub> max <sub>pred</sub> <sup>a</sup> (ml·kg <sup>-1</sup> ·min <sup>-1</sup> )	-.358*	-.358*
Dietary fibre <sup>b</sup> (grams·d <sup>-1</sup> )	-.041	-.016
Energy intake (kcal·d <sup>-1</sup> )	-.294	-.267

<sup>a</sup> transformed by square; <sup>b</sup> log transformed; \* $p < .05$ , \*\* $p < .01$

b) Associations between potential predictors of insulin resistance and indices of insulin resistance when the participants are stratified by gender, weight and puberty status, and physical activity level

After the participants were stratified into gender, pubertal status, weight status and PA subgroups, correlation analyses were conducted for IR predictor variables and HOMA-IR. Significant associations are shown in Table 9.

**Table 9.** The significant relationships between HOMA-IR and potential predictors are presented after adjustment for age and pubertal status and when the participants are stratified into subgroups. \*( $p < .05$ )

	Gender		Pubertal status		Weight Status		PA level	
	<i>B</i>	<i>G</i>	<i>Pre-</i>	<i>Puber.</i>	<i>N</i>	<i>O</i>	<i>HPA</i>	<i>LPA</i>
zBMI		*	*				*	
Waist circum. (cm)		*						
Average PA (counts·min <sup>-1</sup> )								
MVPA (min·day <sup>-1</sup> )	*	*						
VO <sub>2</sub> max <sub>pred</sub> (ml·kg <sup>-1</sup> ·min <sup>-1</sup> )		*						
Stage								*
Fibre (g·day <sup>-1</sup> )	*		*		*			

*B* = boys, *G* = girls, *Pre* = pre-pubertal, *Puber.* = pubertal, *N* = non-overweight, *O* = overweight or obese, *HPA* = high physical activity and *LPA* = low physical activity.

#### *i) Gender*

When the sample was stratified by gender, correlation analyses taking age and pubertal status into account showed several significant ( $p < .05$ ) associations with HOMA-IR in girls: MVPA ( $r = -.453$ ), VO<sub>2</sub>max<sub>pred</sub> ( $r = -.489$ ) were inversely related, while waist circumference ( $r = .644$ ,  $p < .01$ ), hip circumference ( $r = .437$ ), waist to hip ratio ( $r = .527$ ), and zBMI ( $r = .633$ ,  $p < .01$ ) were directly related with HOMA-IR. In boys, only MVPA ( $r = -.544$ ) and dietary fibre intake ( $r = -.611$ ) were significantly associated with HOMA-IR. That is, as MVPA and dietary fibre intake increased, HOMA-IR decreased.

#### *ii) Weight status*

In the non-overweight participants, after adjustment for age and pubertal status, dietary fibre intake was inversely correlated with HOMA-IR ( $r = -.588$ ,  $p < .05$ ).

In the overweight and obese participants, no variables were significantly associated with HOMA-IR. Low power as well as greater variability in HOMA-IR with increasing zBMI may explain the lack of significant associations in the weight status subgroups, particularly in the overweight and obese participants.

*iii) Pubertal status*

After controlling for age, zBMI ( $r=.552$ ,  $p<.01$ ) was directly related, and dietary fibre ( $r=-.419$ ,  $p<.05$ ) and total energy intake ( $r=-.437$ ,  $p<.05$ ) were inversely related with HOMA-IR in pre-pubertal participants. There were no significant associations among the pubertal participants.

*iv) Physical activity level*

In the HPA subgroup, Leger stage ( $r=-.526$ ,  $p<.05$ ) and zBMI ( $r=.492$ ,  $p<.05$ ) were significantly associated with HOMA-IR after adjustment for both age and pubertal status. The higher the Leger stage reached, the lower the HOMA-IR. In contrast, the higher the zBMI value the higher the HOMA-IR. Leger stage was also negatively associated with fasting insulin ( $r=-.497$ ,  $p<.05$ ). There were no significant associations in the LPA subgroup.

*4.5 Multiple regression analysis to estimate insulin resistance*

In the stepwise regression procedure used to predict IR, zBMI and pubertal status were positively associated and MVPA was negatively associated with HOMA-IR ( $p<.001$ ). Combined, these variables explained 46% of the variance in HOMA-IR ( $R^2=46$ ). Table 11 provides the multiple regression model with HOMA-IR as the dependent variable.

**Table 10.** Stepwise multiple regression with HOMA-IR as the dependent variable (n=39).

<i>Independent predictors</i>	<i>Coefficient (B) ± SE</i>	<i>Standardized coefficient (β)</i>	<i>P</i>
Constant	.351		.057
Pubertal status	.171 ± .072	.314	.023*
zBMI	.076 ± .033	.304	.028*
MVPA (min·day <sup>-1</sup> )	-.003 ± .001	-.319	.024*
Sex	.013		.919
Age (y)	-.006		.970
Waist circumference	-.201		.431
Hip circumference	-.298		.214
Waist:Hip	.075		.587
Average physical activity intensity (counts·min <sup>-1</sup> )	-.008		.961
Sedentary activity (min·day <sup>-1</sup> )	-.007		.960
VO <sub>2</sub> max <sup>a</sup> (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	-.066		.692
Energy intake (kcal·day <sup>-1</sup> )	-.204		.115
Carbohydrate intake <sup>b</sup> (grams·day <sup>-1</sup> )	-.092		.474
Dietary Fibre (grams·d <sup>-1</sup> )	.060		.645
Sugar sweetened beverage <sup>b</sup> (mL·week <sup>-1</sup> )	.143		.292

R<sup>2</sup>=.46; SE = standard error of estimate = .206; \*p<.001; <sup>a</sup>squared, <sup>b</sup>log transformed

The value of the multiple correlation coefficient was found to be R=.675 indicating a relationship of moderate strength. The significance value of the F statistic is less than 0.05 (F=9.77, p<.001), which means that the variation explained by the model is not due to chance. Although MVPA is inversely related to HOMA-IR, pubertal status, zBMI and MVPA all contribute roughly the same weight to the prediction equation (β=.314, .304 and -.319, respectively). In particular, a 30 minute

increment in MVPA was associated with a 23% change (increase or decrease) in HOMA-IR (Figure A3 in Appendix 11).

## Chapter 5: Discussion

The uniqueness of this study was the availability of measures of insulin resistance (IR) together with accelerometer derived measures of physical activity (PA) in a First Nations paediatric population. To our knowledge, the current study was the first to examine the cross-sectional relationship between accelerometer derived habitual PA and IR in a paediatric Aboriginal population. It was also the first to examine the cross-sectional relationship between habitual PA, whether measured objectively or by questionnaire, and IR in a paediatric First Nations population.

The main drawback of the cross-sectional design of this study is that it only provides a snapshot of what is actually occurring. Therefore errors in measurement, in determining habitual PA for example, could have skewed our findings. This is a major reason why accurate objective measures of PA, such as accelerometers, are so valuable to contemporary PA research. The advantage of studying this relationship by cross-section is that the study is not limited by a short exposure to a PA program (8 to 12 weeks).

The precision of accelerometer derived measures of habitual PA energy expenditure in children is superior to subjective methods (Brage et al., 2004). There are some limitations however and they should be noted. Cycling, swimming and weight bearing activities, for example, are not captured by accelerometers. It is believed though that estimating the amount of time engaged in these activities would not have affected our conclusions as the opportunities to swim and cycle in Hartley Bay and Kitkatla were very limited. As well, accelerometers do not account for the relative increase in energy expenditure with increasing body size. Until procedures

for adjusting for body size are identified however, it has been recommended that age-specific procedures are used (Esliger et al., 2005).

### *5.1 Unique geographic location*

Hartley Bay and Kitkatla are rural and remote coastal villages in northern British Columbia. Owing to their remote geographic location, significant barriers to PA and proper consistently available nutrition exist. The proximity to wildlife restricts outdoor play activities due to inherent risks associated with aggressive wildlife, making it dangerous for children to play outdoors or far from home or school. As well, the relative isolation of the communities (only accessible by plane and boat) can make it difficult and expensive to import fresh fruits, vegetables and dairy products. This unique environment distinguishes the current study from others that have investigated type 2 diabetes (D2) risk factors in youth living in more accessible urban and rural areas.

### *5.2 Representativeness*

The First Nations Regional Longitudinal Health Survey 2002/03 (RHS 02/03) is the most comprehensive nationally representative health survey conducted with First Nations people. Using the RHS 02/03 as a reference, the prevalence of overweight and obesity in both boys and girls of the present study, 9 to 11 yrs of age was 19.1%, compared to 28.8% and 26.4% for boys and girls in the RHS 02/03. Conversely, the prevalence of overweight and obesity among 12 to 17 yr old adolescents in our sample were greater, 35.7% and 28.6% respectively, compared to 28.1% overweight and 14.1% obese in the RHS 02/03.

The prevalence of measures of adiposity among First Nations children in the current sample are similar (overweight) and 2.4 times greater (obesity), than the prevalence reported among Canadian children in general (excluding the territories) (Shields, 2006). Among First Nations adolescents in the current sample, the proportion of overweight and obesity is 1.8 and 3.2 times greater, respectively, than in Canadian adolescents (Shields, 2006). Given the exceptionally high prevalence of overweight and obesity and the strong link between adiposity and IR (McMurray et al., 2000), the children and adolescents in this cohort are at a high risk of developing D2.

Reliable impaired fasting glucose (IFG) and IR prevalence data are not available in the RHS 02/03. Cross-sectional data from a remote Aboriginal community in northern Manitoba (n=719, 4-19 yrs) however serves as a good reference population with which to compare our sample (Young et al., 2000). Young et al. (2000) determined that 3.8% of the children and adolescents in the community had either IFG (n=19) or clinical D2 (n=8). Similarly, 2.5% of the participants in our sample had IFG (n= 1) ( $\geq 6.1$  mmol/L). Using the most current international criterion for IFG (5.6 to 6.9 mmol/L) however, this prevalence increased to 18% (n=7). To date, nationally representative data on the prevalence of IR among Canadian youth are not available.

Higher rates of overweight and obesity among the current participants compared to those living in less remote communities, and the elevated risk of developing D2 among First Nations adults (Young, 2000), suggest that youth living in Hartley Bay and Kitkatla may be at an increased risk of developing D2. Similarly,

First Nations youth living in rural and remote communities in Manitoba are at an increased risk of developing D2. Specifically, between 1996 and 2000, Dean et al. (2003) determined that the majority of paediatric D2 patients in Manitoba (80%) lived in rural or remote areas. Furthermore, it has been suggested that D2 risk and prevalence may increase with the degree of isolation (Johnson et al., 2002), highlighting the importance of implementing culturally-appropriate and sustainable PA programs for youth in rural and remote First Nations communities.

### *5.3 Genetic susceptibility*

It is generally believed that the prevalence of overweight and obesity and IR among Aboriginal youth is the result of both environmental and genetic factors. The ‘thrifty gene’ theory states that ethnic minorities are genetically predisposed to weight gain and IR (Neel, 1962). It proposes that in response to rising blood glucose levels, Aboriginals, along with other ethnic minorities, rapidly produce and secrete insulin, facilitating the storage of glucose in the form of triglycerides in fat cells – a distinct advantage in times of food shortage. Unfortunately, the increased availability of energy-dense foods and the recent trend towards inactivity has turned this metabolic phenotype into a clear disadvantage for First Nations people. First Nations youth are especially at risk because D2 can develop very quickly, in just a few years, in children (Goran et al., 2003).

*5.4 Moderate to vigorous intensity physical activity is associated with insulin resistance*

The main finding of this study was that fasting insulin and HOMA-IR were negatively associated with moderate to vigorous intensity physical activity (MVPA). The inverse relationship between MVPA and IR persisted even after adjustment for total and central adiposity, suggesting that MVPA influences IR separate from its effect on adiposity. This hypothesis is supported by youth training studies conducted by Nassis et al. (2005) and Kahle et al. (1996) in which PA improved IR in the absence of changes in body weight and percent body fat.

In the only other cross-sectional study examining the relationship of PA and IR in Aboriginal youth, Bunt et al. (2003) found that in 10 yr old Pima Indian children, there was a significant association between objectively measured PA (doubly-labelled water method) and an index of insulin sensitivity, but this was lost after adjustment for weight or percent adiposity (Bunt et al., 2003). The lack of association after correcting for adiposity may be explained by the small sample size (n=33) or by the limited range of PA levels in the cohort.

A growing number of paediatric studies have reported inverse relationships between PA and IR after adjustment for adiposity (Rizzo et al., 2008; Krekoukia et al., 2007; Manios et al., 2007; Brage et al., 2004; Schmitz et al., 2002; Ku et al., 2000). Other studies have demonstrated improvements in IR following structured exercise interventions (Ku et al., 2000; Matsui et al., 1998). Ferguson et al. (1999) reported that the cessation of regular PA (for 4 months after a 4 month training period) reversed training-induced improvements in IR in 7 to 11 yr old obese African

American and Caucasian children. From these correlational and interventional studies there is substantial evidence that PA is associated with improved IR. Our findings agree with those of others and support the hypothesis that MVPA may protect against IR, thus reducing D2 risk in First Nations youth, even in the absence of changes in body composition. As well, there may be additive effects of increasing PA and reducing adiposity, especially central adiposity (Goodyear and Kahn, 1998).

### *5.5 Predicting HOMA-IR in First Nations youth*

When all the potential predictors of HOMA-IR were considered, this study demonstrated that pubertal status, total body adiposity and MVPA were the most influential variables in the prediction of HOMA-IR in First Nations youth. Specifically, a 30 minute increment in daily MVPA corresponded to a 23% reduction in HOMA-IR (Equation A12).

The findings from previous studies suggest that the impact of MVPA on IR may be even stronger in the First Nations participants with elevated fasting insulin levels and IR. This is because previous training and cross-sectional studies have shown that the greatest improvements in IR are usually reserved for children and adolescents with elevated fasting insulin and IR (Rizzo et al., 2008; Kang et al., 2002; McMurray et al., 2000). Given this ‘floor’ effect, in which increasing the ‘dose’ of PA leads to smaller and smaller reductions in IR, MVPA may have an even larger effect on IR in the First Nations participants in the current sample at higher risk of developing D2 (i.e. the less active and overweight and obese participants with

elevated fasting insulin and IR). Due to a small sample size however this differential effect could not be confirmed.

After controlling for potential confounders, Rizzo et al. (2008) revealed significant associations between physical activities of varying intensities and IR in adolescents in Sweden and Estonia, Krekoulia et al. (2007) found a link between total PA (minutes·day<sup>-1</sup>) and IR in a group of school-aged Greek children, while Manios et al. (2007) found no significant associations between PA and IR. The lack of a significant association in Manios et al. (2007) was attributed to the inherent methodological difficulties in measuring self-reported PA (i.e. misunderstood instructions, competing memories, and social desirability).

The current regression model does a good job of predicting HOMA-IR in this unique population. It is optimized for the current sample though and might differ for another group with different characteristics. Having said that, to our knowledge, it is the first regression model to link objectively measured PA and IR in a paediatric First Nations population and provides much needed empirical evidence of the dose-response relationship between habitual PA and IR in this cohort.

#### *5.6 Comparing the relative contribution of physical activity to insulin resistance in First Nations versus Caucasian children and adolescents*

Amidst differences in methodology and participant characteristics, standardized PA regression coefficients can provide insight into the relative effect of habitual PA on IR in First Nations youth as compared with Caucasian populations. This is important given that Canada's Physical Activity Guidelines for Children and

Youth are largely-based on data from Caucasian studies (Bar-Or, 1999). As well, it has been suggested that First Nations youth, along with other minority youth, may require different amounts of PA than Caucasian youth for health benefits (Goran et al., 2002).

Brage et al. (2004) reported a standardized PA coefficient after adjusting for potential confounders, although the PA variable used in the regression model (average PA intensity) was different than the one utilized in the present study (MVPA,  $\text{min}\cdot\text{day}^{-1}$ ). The standardized PA coefficient in Brage et al. (2004) ( $\beta=-.179$ ) was approximately half the weight of the coefficient reported in this study ( $\beta=-.319$ ). This was expected given that MVPA is known to influence IR to a greater extent than measures of average PA intensity (Rizzo et al., 2008).

After controlling for sex, country, pubertal status and waist circumference, Rizzo et al. (2008) determined that PA of varying intensities (moderate-, vigorous-, moderate to vigorous and average PA intensity) were inversely correlated to HOMA-IR. Specifically, the standardized MVPA coefficient was  $\beta=-.141$ , again approximately half the weight reported for MVPA in the current study ( $\beta=-.319$ ). It is not prudent to compare these standardized coefficients however because of key differences in participant characteristics between the two studies. For instance, just 2% of Rizzo et al.'s (2008) subjects were pre-pubertal compared to the majority of the participants in the current study (62%) (Table A1 in Appendix 8). As well, the prevalence of overweight or obesity was 10% in the Rizzo et al. (2008) sample compared to 49% in the current study (Table A1 in Appendix 8).

Standardized coefficients can be useful when comparing the relative contributions of habitual PA to IR. Due to differences in methodology and participant characteristics however, the task of deciding on the relative importance of habitual PA in different ethnic groups is difficult. To this end, bi-racial studies examining the association of habitual PA and IR are necessary for the development of evidence-based PA guidelines for First Nations youth.

#### *5.7 How does physical activity improve insulin resistance?*

Research suggests that exercise-induced improvements in IR and glucose homeostasis are largely due to the overlapping effects of individual exercise bouts and not necessarily to chronic adaptations to training (LaMonte et al., 2005; Goodyear & Kahn, 1998). The greatest improvements in glucose control, therefore, seem to occur through participation in an adequate dose of PA on a regular, perhaps daily, basis.

#### *5.8 Intensity of physical activity influences insulin resistance*

It has been determined that aerobic activities of varying intensities (light, moderate and vigorous) can improve IR (Rizzo et al., 2008; Mayer-Davis et al., 1998; Kahle et al., 1996). Intervention studies have also determined that strength training has the potential to improve IR in youth (Treuth et al., 1998). It is suggested though that vigorous-intensity aerobic activity has the greatest impact on IR (Rizzo et al., 2008; LaMonte et al., 2005). It is believed that the exaggeration of vascular conductance and blood flow and the high rate of muscle contraction during vigorous

training improves IR and stimulates the recruitment of GLUT4 proteins to a greater extent than lower intensity aerobic activities or strength training (Goodyear & Kahn, 1998). Vigorous-intensity aerobic PA may be especially effective in reducing adiposity as well, which may in turn lead to favourable changes in IR (Hunter et al., 1998). Moreover, vigorous-intensity aerobic PA has the added benefit of improving fitness, thus making low-intensity exercise less difficult and more easily tolerated. These features may explain why vigorous-intensity PA is most commonly related to lower IR and a healthy metabolic profile while the effect of light- to moderate-intensity activities are less conclusive (LaMonte et al., 2005).

In contrast to findings from Rizzo et al. (2008) and Anderson et al. (2006), average PA intensity ( $\text{counts}\cdot\text{minute}^{-1}$ ) was not linked to IR in the current study. Anderson et al. (2006) conducted a robust paediatric study on the dose-response relationship between PA and health in 9 and 15yr olds from Denmark, Estonia, and Portugal ( $n=1732$ ). They determined that the likelihood of having a high cardiovascular risk score (based on several cardiovascular risk factors including blood pressure, triglycerides, total cholesterol/HDL ratio, IR, the sum of four skinfolds, and aerobic fitness) increased in a clear dose-response manner when moving from the lowest to the highest PA quintile. This was found for all PA variables, including average PA intensity and time spent in MVPA.

Average PA intensity is a valuable summary variable because it can be easily compared between studies. However, the use of this variable often results in the loss of important information about the intensity of activity. By integrating light, moderate and vigorous intensity activities into a single summary variable, the strong

influence of vigorous intensity activity on IR is diluted, making the relationship more difficult to quantify. This is especially true given the current study's small sample size. These factors may explain the lack of a significant association between average PA intensity and IR.

#### *5.9 Cardio-respiratory fitness is associated with insulin resistance*

Consistent with other studies (Manios et al., 2007; Krekoukia et al., 2007) MVPA was a stronger predictor of HOMA-IR than CRF. Habitual PA, the principle determinant of CRF (LaMonte et al., 2005), is generally related to lower IR and a healthy metabolic profile, while studies using CRF as the main outcome are less conclusive (Goran et al., 2003). Other determinants of CRF, including age, sex, health status and genetics, likely contribute to the inconsistent findings. The indirect, predictive measure used to reflect CRF, may have affected our findings as well.

#### *5.10 Elevated total and central adiposity are associated with insulin resistance*

Similar to studies in Caucasian, South Asian, African American and Native American children, elevated total adiposity of the present participants was significantly related to increased levels of IR. The significant associations between zBMI and HOMA-IR in Caucasian children ranged from  $r=.40$  to  $.70$  (Manios et al., 2007; Krekoukia et al., 2007; Moore et al., 2006), consistent with that found in the current study ( $r=.44$ ).

Although there are several limitations inherent in using the BMI to estimate body fat (i.e. BMI does not differentiate adipose from lean tissue and does not take

body fat distribution into account) it provides a good estimate of total adiposity and was the most appropriate method available in the current study. The limitations of the BMI however highlight the value of using other measures of adiposity, such as waist circumference, in addition to BMI, when examining the health complications of obesity.

Of the 3 measures of central obesity in this study, waist circumference was the only obesity variable found to have a significant correlation with fasting insulin and HOMA-IR (Table 9). This finding supports those reported for school-aged Greek children (Manios et al., 2007) and for participants in the Bogalusa Heart Study (Freedman et al., 1999), in which similar significant relationships were observed. The distribution of fat, and not only total adiposity, appears to be an important parameter of obesity among First Nations youth.

Although both waist circumference and zBMI were independently associated with IR, only zBMI remained significantly correlated with HOMA-IR in the stepwise regression analysis. Similarly, Lawlor et al. (2005) and Goran et al. (2001) reported that while central obesity was associated with fasting insulin, it was not related to IR. These findings differ from other paediatric studies that determined that waist circumference, an effective marker of visceral and subcutaneous abdominal adiposity (Taylor et al., 2000), is a stronger predictor of IR and cardiovascular risk than BMI (Manios et al., 2008; Krekoukia et al., 2007; Savva et al., 2000).

The association between central obesity and elevated fasting insulin might be due to low hepatic insulin clearance as a result of exposure of the liver to free fatty acids from central adipose tissue (Svedberg et al., 1990). Also, the association

between central obesity and IR could be attributed to greater intra-myocellular fat accumulation, as a result of high levels of circulating free fatty acids from central adipose tissue (Weiss et al., 2005).

While more research is needed, visceral adipose tissue, possibly due to its proximity to the liver, is believed to influence IR to a greater extent than subcutaneous abdominal fat (Goran et al., 1999). The hypothesis that visceral fat is relatively lower in children and adolescents compared with adults (Goran et al., 1999) might explain why the relationship between waist circumference and IR was slightly weaker than between zBMI and IR in this cohort. Further study on the health risks associated with total versus central adiposity should be conducted to clarify the role body fat distribution plays in the development of IR and cardiovascular disease in First Nations youth.

#### *5.11 Dietary habits and insulin resistance*

In accordance with Liese et al. (2005), dietary fibre intake of the First Nations participants in the present study was associated with lower HOMA-IR values. This association was seen in boys, in non-overweight participants and in the pre-pubertal children. An increased consumption of dietary fibre such as whole grains, and fresh fruits and vegetables, has been previously shown to help maintain normal glucose tolerance and decrease the degree of compensatory hyperinsulinemia in insulin resistant individuals (Reaven, 2005). Diabetes prevention programs intending to curb the development of D2 in First Nations populations, particularly those in remote

locations, should consider the unique challenges faced in obtaining consistent access to high-fibre foods.

Similar to Liese et al. (2005) but in contrast with Manios et al. (2007), sugar intake was not significantly associated with HOMA-IR in our First Nations participants. It is well documented however, that high-glycemic foods (i.e. juice, soda, cookies) are associated with a greater release of insulin and glucose into the blood after a meal which can lead to excessive weight gain and IR, especially in susceptible youth (Slyper, 2004). For this reason, it would be prudent to restrict or reduce the amount of high-glycemic foods and drink consumed by First Nations youth, particularly sugar-sweetened beverages, consistent with standard healthy dietary practices (Eating Well with Canada's Food Guide – First Nations, Inuit and Metis, 2007).

#### *5.12 Comparisons between the subgroups*

Comparison between subgroups revealed that participants classified as non-overweight and in the high physical activity (HPA) subgroup had lower fasting insulin and HOMA-IR values than those classified as overweight or obese and in the low physical activity (LPA) subgroup, respectively. Specifically, 80% of the participants with measurable IR were overweight or obese. This finding is in accordance with those reported by Valerio et al. (2006), who, using HOMA-IR > 2.5 as the threshold for 'normal', found that the prevalence of IR was lower in non-overweight children (3%) than in obese children (40.8%).

Furthermore, 85.7% of the current participants with IFG were classified in the LPA subgroup. This finding is similar to data from Schmitz et al. (2002) who reported that in 10 to 16 yr old children IR was significantly higher in the 2<sup>nd</sup> compared to the highest PA quartile.

Gender-specific analysis revealed that increases in MVPA correspond to reductions in HOMA-IR in both girls and boys ( $r=-.453$  and  $-.544$ , respectively,  $p<.05$ ). As in Krekoukia et al. (2007), the girls in this sample were significantly less active and less aerobically fit than the boys, possibly explaining the higher prevalence of overweight and obesity among girls (61.87% in the girls vs. 31.25% in the boys) (Table 3).

HOMA-IR and fasting insulin values were not significantly different in the boys and girls of this First Nations study. This is in contrast with other large studies that have measured IR using the gold standard hyperinsulinemic-euglycemic clamp (IS<sub>EU</sub>) (Moran et al., 1999). This may have been influenced by low participant numbers. It is possible that greater statistical power may have altered our findings. Although IR was similar in the boys and girls, the girls were more overweight and obese, which invariably puts them at an increased risk of developing D2. Interventions to increase PA among First Nations girls in particular are therefore warranted.

### *5.13 Implications for Canada's Physical Activity Guidelines for Children and Youth*

Owing to a lack of well controlled PA studies, there is currently no consensus on the dose-response relationship between PA and health in children and

adolescents. Consequently, it has been difficult to set minimal and optimal PA targets for youth.

Despite the lack of dose-response studies, the findings of Anderson et al. (2006) provide insight into what minimal and optimal PA recommendations might be for Caucasian children. They suggest that some health benefits exist at lower levels of PA, but that higher levels of PA will result in additional health benefits. Anderson and associates (2006) also found that 9 yr old children accumulating less than 92 minutes of MVPA per day had increased cardiovascular risk (of which IR was the central feature) compared to children accumulating more than 167 minutes of MVPA per day. Therefore, for Caucasian children, PA recommendations of at least 90 minutes of moderate-intensity activity per day may be inadequate to prevent IR.

The First Nations children in this study may require more than the recommended 90 minutes of MVPA per day to prevent IR as well. First Nations children may actually require more PA than their Caucasian counterparts as they have reported higher fasting insulin levels and greater IR than Caucasians, even after adjustment for adiposity (Dean et al., 1998).

While the majority (93%) of the participants in this study appeared to be meeting Canada's Physical Activity Guidelines for Children and Youth ( $\geq 90$  minutes daily MVPA), almost half (49%) were overweight or obese and therefore at a high risk of developing D2. Also, the mean time spent in MVPA was 108 minutes among the participants with IFG and 123 minutes for the participants with measurable IR. These data suggest that a gap exists between the amount of PA that is

being recommended and the amount that is required for metabolic health in First Nations youth.

It is important to note the possibility that the participants in the current study were more active than usual because of the unusually warm and dry summer weather. Also, the recent implementation of an innovative school based activity program may have encouraged the children to be more active than normal.

It is recognized that a prescription of more than 90 minutes of PA activity per day can be intimidating, especially for children and adolescents who are currently very inactive. The challenge is even greater for those living in remote communities in which safe areas for spontaneous play are limited and weather can be a significant barrier to regular PA. From a behavioural perspective, suggesting a hard to attain target might actually discourage participation in PA. Instead First Nations youth should be encouraged to increase participation in regular MVPA (i.e. playing outside, brisk walking) by 30 minutes on most days of the week as in Canada's Physical Activity Guidelines for Children and Youth (Health Canada and the Canadian Society for Exercise Physiology, 2002a; Health Canada and the Canadian Society for Exercise Physiology, 2002b) regardless of their current levels of PA. In remote locations where outdoor play may be restricted due to lack of light, harsh weather conditions or aggressive wildlife, communities should be encouraged to provide additional access to school/community facilities and programs.

As a 30 minute increase in MVPA corresponded to an improvement in HOMA-IR of approximately 23% in this cohort (Figure A3 in Appendix 11) and taking into consideration that the prediction model only accounts for 46% of the

variability in HOMA-IR, our estimates indicate that if every participant in the present study increased their amount of daily MVPA by 30 minutes there would be no prevalence of IR in the current sample of pre-pubertal children (from 12.5%) and a 20% reduction in prevalence of IR among pubertal adolescents (from 46.6%). The prospect of implementing culturally-appropriate PA initiatives in isolated, closely-knit communities such as the ones in Hartley and Kitkatla is exciting given the potential health benefits of even just a small amount of daily PA.

#### *5.14 Recommendations*

In addition to encouraging First Nations youth to increase their amount of daily MVPA (i.e. brisk walking, play, strength training) by 30 minutes, we recommend that PA interventions target pre-pubertal First Nations children and First Nations girls in particular. Lifestyle intervention strategies as opposed to structured exercise programs have produced improvements in IR in Aboriginal adolescents in the past (Ritenbaugh et al., 2003) and are highly recommended. In younger children, the emphasis should be on general physical activities (games, play, climbing, gymnastics, etc.) and in older children the emphasis should be on prescriptive physical activities including organized sport, outdoor education and structured resistance-training or walking programs (Malina, 1991). Incorporating traditional activities such as dancing, hunting, fishing, gathering sea weed, and snowshoeing, in addition to encouraging active commuting and random play, will be important for future prevention of D2 in this population.

Treuth et al. (1998) examined the effect of strength training on metabolic risk in paediatric populations and found that resistance training performed for 20 minutes, 3 days a week for 5 months led to increases in strength, improvements in glucose tolerance and insulin levels that approached significance, and stopped visceral fat accumulation. Since First Nations youth are known to store more fat centrally as a proportion of total adiposity (Lohman et al., 2000; Young et al., 2000), a strength training intervention may be particularly useful among First Nations youth as an alternative approach to reducing adiposity.

Thoughtful and appropriate interventions that promote PA and decrease physical inactivity are valuable because they have the capacity to influence several important physiological outcomes including total and central adiposity and IR, and attenuate the development of D2 without the use of drugs or the implementation of a strict and hard to follow diet.

### *5.15 Future Directions*

Well designed dose-response studies investigating the influence of different amounts and types of PA on health in First Nations youth will help determine minimal and optimal amounts of PA as well as the intensity of PA required for good health. A bi-racial cross-sectional study examining the relationship between PA and IR in First Nations versus Caucasian youth would clarify whether Caucasian and First Nations youth require the same amount of PA for health benefits and whether Canada's Physical Activity Guidelines for Children and Youth should be tailored to meet the needs of First Nations youth. These analyses should be performed using a

variety of PA outcome variables including light, moderate and vigorous intensity PA, as well as MVPA, average PA intensity, and 5 and 10 minute bouts of MVPA.

In order to focus PA interventions, patterns of PA, including the times of day and week in which the children and adolescents are the least active should be identified. For example, if the participants appear to be less active on weekend days, interventions should aim to engage children and adolescents in physical activities on the weekends.

Validation studies to more accurately convert accelerometer cut-off points into physiological intensities are needed. Also, future research to define age-specific waist circumferences above which risk of cardiovascular disease markedly increases in this cohort is warranted given the strong link between central adiposity and IR. Finally, further analysis investigating the influence of habitual PA on the clustering of cardiovascular disease risk factors in First Nations youth, instead of just on a single risk factor, will enhance the understanding of the important therapeutic role PA may play in preventing D2 and CVD in this vulnerable population.

### *5.16 Conclusions*

Active and lean First Nations children and adolescents have lower HOMA-IR values. The beneficial influence of PA on insulin action, and thus on reduction of D2 risk, appears to be operative in childhood and adolescence in First Nations youth. Since pubertal IR has the potential to advance pre-diabetes to full blown D2, the time before puberty is important for the prevention of D2 related health complications. Increasing the amount and intensity of daily PA among pre-pubertal children through

preventative PA initiatives will ensure that they are in a more favourable position as they enter puberty. As well, engaging children in physical activities early in life will increase the likelihood that they will maintain healthy PA behaviours through adolescence and adulthood. The development of culturally-appropriate interventions to increase PA is likely to be of paramount importance if D2 is to be averted in First Nations populations. Sustainable PA programs will be particularly important for those living in geographically remote communities with limited structured, year-round PA recreational opportunities.

## APPENDICES

## Appendix 1:

**International cut-off points for body mass index for overweight and obesity by sex between 2 and 18 years. Obtained by averaging data from Brazil, Great Britain, Hong Kong, Netherlands, Singapore and the United States**

Age (years)	Body mass Index 25 kg/m <sup>2</sup>		Body mass Index 30 kg/m <sup>2</sup>	
	Males	Females	Males	Females
2	18.41	18.02	20.09	19.81
2.5	18.13	17.76	19.80	19.55
3	17.89	17.56	19.57	19.36
3.5	17.69	17.40	19.39	19.23
4	17.55	17.28	19.29	19.15
4.5	17.47	17.19	19.26	19.12
5	17.42	17.15	19.30	19.17
5.5	17.45	17.20	19.47	19.34
6	17.55	17.34	19.78	19.65
6.5	17.71	17.53	20.23	20.08
7	17.92	17.75	20.63	20.51
7.5	18.16	18.03	21.09	21.01
8	18.44	18.35	21.60	21.57
8.5	18.76	18.69	22.17	22.18
9	19.10	19.07	22.77	22.81
9.5	19.46	19.45	23.39	23.46
10	19.84	19.86	24.00	24.11
10.5	20.20	20.29	24.57	24.77
11	20.55	20.74	25.10	25.42
11.5	20.89	21.20	25.58	26.05
12	21.22	21.68	26.02	26.67
12.5	21.56	22.14	26.43	27.24
13	21.91	22.58	26.84	27.76
13.5	22.27	22.98	27.25	28.20
14	22.62	23.34	27.63	28.57
14.5	22.96	23.66	27.98	28.87
15	23.29	23.94	28.30	29.11
15.5	23.60	24.17	28.60	29.29
16	23.90	24.37	28.88	29.43
16.5	24.19	24.54	29.14	29.56
17	24.46	24.70	29.41	29.69
17.5	24.73	24.85	29.70	29.84
18	25	25	30	30

(Cole et al., 2000)

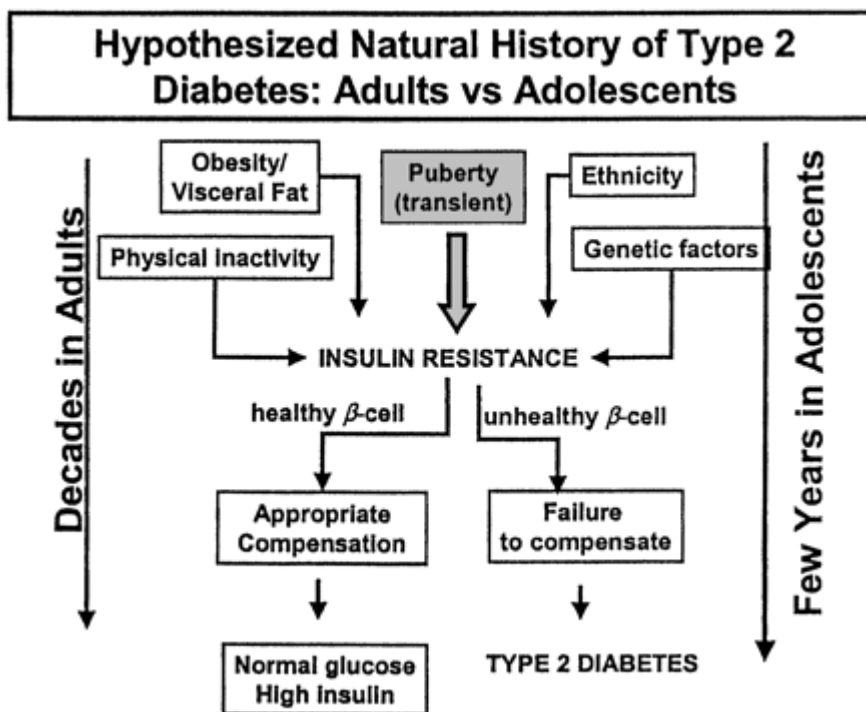
**Appendix 2:****The diagnostic criteria for normal glucose homeostasis, impaired fasting glucose and diabetes.**

	Normal Fasting Glucose	Impaired Fasting Glucose	Diabetes Mellitus
Fasting Plasma Glucose (mmol/L)	3.9 – 5.5	$\geq 5.6$	$\geq 7.0$

(Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003)

## Appendix 3:

Schema of the proposed pathophysiology for the development of type 2 diabetes.



(Goran, Ball, & Cruz, 2003)

#### **Appendix 4:**

##### **Step-by-step description of the accelerometer data cleaning and reduction procedures employed in the current study.**

The raw data files obtained from the ActiLife Lifestyle Monitor Software program were processed using KineSoft software (v2.0.90), a software program designed especially for Action Schools! BC by Dale Esliger and Eric Finley of the University of Saskatchewan. The raw data files were sorted and prepared before being run through the program. For a weekday to be considered valid there must have been at least 10 hrs of activity recorded. For a weekend day to be considered valid, the participant must have worn the ActiGraph for at least 60% of the average wear time for similarly aged participants for that day (Masse et al., 2005). This criterion was incorporated because of the large observed differences in sleep time between age groups on the weekends.

##### a) Spurious data

In order to distinguish motionless data from zeros recorded when the monitor had been taken off, the data needed to be cleaned. Other studies have automatically excluded gaps in the data (prolonged strings of zero counts) greater than 10 minutes (Brage et al. 2004) on the basis that, in children, the bulk of motionless data is accumulated in bouts of 10 minutes or less (Esliger et al., 2005). Since the vast majority of participants recorded numerous strings of zero counts greater than 10 min each day, and given the population's generally sedentary lifestyle, we concluded that the monitor was likely not being taken off and put back on this often every day. Consequently, it was decided to interpret only strings of zeros greater than the

average longest motionless bout for similarly aged children as ‘time not worn’. Esliger et al. (2005) used this approach when they determined that motionless bout data of 20 or more consecutive minutes was biologically implausible in a group of 115 rural children age 8-13yrs. While the most frequent longest motionless bout was about 20 min, a small number of extremely long bouts of inactivity (i.e. 2-3hrs long) raised the average longest motionless bouts to 67 min in grades 4-6, and 63 min in grades 7-12. Strings of zeros longer than these averages were uncharacteristic and deemed biologically implausible and thus were excluded from the analysis. Reducing data in this way helped to avoid excluding true bouts of inactivity.

The data were also examined for spurious outputs above the range of biological plausibility. Data from a study of 115 rural children age 8 to 13yrs show values as high as 31 346 counts/min as possible (Esliger et al., 2005). Outputs greater than 7837 counts/15s then were examined to determine physiological possibility. The magnitude of the data points surrounding these high outputs and common sense guided the screening process. No high data points were considered to be biologically impossible and thus none were excluded. Screening spurious data ensures that the outcome variables are not contaminated by extreme values that are the result of improper use and manipulation, or faulty monitors.

#### b) Determining On and Off times

In order for KineSoft to calculate output variables, ‘monitor on’ and ‘monitor off’ times needed to be inputted for each day. Exact on and off times were identified in the ActiLife output, highlighted yellow and recorded in 24 hr format. The first possible time point for all the participants was 4 a.m. the morning after the

ActiGraphs were distributed. The last possible end point for everyone was 23:58:30 on the last day of the week.

- 1) If there was no missing time during the day (i.e. no extended periods of zeros in the data file) then we located the first and last data points on the graph and recorded the exact time from the output.
- 2) If on one or more occasions there was a string of zeros equal or shorter than the average longest motionless bout and not near the on or off times, we located the first and last data points on the graph and recorded the exact time from the output spreadsheet.
- 3) If there was missing data greater than the average longest motionless bout, we recorded the start and end times of the missing data as well as the on and off times for that day.
- 4) If there was missing data that occurred near the beginning or end of the day, and if the extra counts occurred within 20 minutes of the last count then the counts were accepted as valid. If the counts occurred more than 20 minutes from the last counts then they were only accepted as valid counts if there were 8 or more epochs of data over a 4 min period.

When trying to determine on and off times when the participant wore the accelerometer through the night we considered the pattern of counts during sleep (i.e. magnitude and frequency) and used common sense to figure out if a count was physiologically likely.

c) Determining a valid day

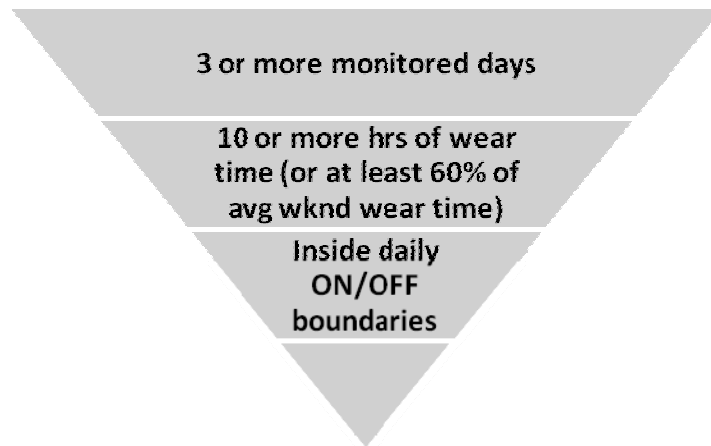
As previously stated, a weekday had to have at least 10 hrs of monitored activity to be considered a valid day. While different criteria have been used to identify the minimal wear requirement for a valid day, 10 hrs of wear time is most often used (Brage et al., 2004). To our knowledge no evidence in the literature exists supporting a standardized minimal wear requirement for a valid day (Masse et al., 2005). Since there was great variability in time worn on weekend days (i.e. the older participants generally slept in later on the weekends thus accumulating less wear time) and since sleeping time seemed to differ between school days and weekend days in general, we based the criteria for a valid weekend day on percent of awake time (60%) as this took into account intra-individual and intra-day variability in sleeping patterns (Masse et al., 2005). Basing the weekend day criterion on percent of awake time enabled us to capture the most data possible. A limitation of reducing the data in this way is that participants who accumulated more wear time during the weekend days (i.e. didn't sleep in more than during the school-week) are also able to accumulate more total time in MVPA and in sedentary activities.

d) Determining On and Off boundaries

Due to variability in the length of time worn and time of day worn the monitor must have been put on and taken off within 2 standard deviations of the average on and off times in similarly aged participants. If a participant put the monitor on too late or took it off too early, the day was not considered valid. If a participant put the monitor on too early or took it off too late, the outside boundary of the 2 standard deviation window was used instead so as not to exclude

participants who wore the monitor too long. Once we determined the number of valid days for a participant, the files were sorted (binned) and scripted. Figure A1 illustrates the criteria for including participants in the analysis.

**Figure A1.** Criteria for accepting accelerometer data.



e) Binning Files

Files were sorted according to the number and type (weekday or weekend day) of valid days they contained (Figure A2).

*Hartley Bay Bin System*

Bin 1 - 6.5 valid days  
 Bin 2 - 6 valid days (missing Monday)  
 Bin 3a - 5.5 valid days (missing wk day)  
 Bin 3b - 5.5 valid days (missing wknd day)  
 Bin 4a - 5 valid days (missing Monday and wk day)  
 Bin 4b - 5 valid days (missing Monday and wknd day)  
 Bin 5a - 4.5 valid days (missing wk day and wknd day)  
 Bin 5b - 4.5 valid days (missing 2 wk days)  
 Bin 5c - 4.5 valid days (missing 2 wknd days)  
 Bin 6a - 4 valid days (missing Monday, wk day and wknd day)  
 Bin 6b - 4 valid days (missing Monday and 2 wk days)  
 Bin 6c - 4 valid days (missing Monday and 2 wknd days)  
 Bin 7a - 3 valid days (missing 1 wk day and 2 wknd days)  
 Bin 7b - 3 valid days (missing 2 wk days and 1 wknd day)  
 Bin 7c - 3 valid days (missing 3 wk days)  
 Bin 8 - < 3 valid days

*Kitkatla Bin System*

Bin 1 - 5.5 valid days  
 Bin 2 - 5 valid days (missing Tuesday)  
 Bin 3a - 4.5 valid days (missing wk day)  
 Bin 3b - 4.5 valid days (missing wknd day)  
 Bin 4a - 4 valid days (missing Tuesday and wk day)  
 Bin 4b - 4 valid days (missing Tuesday and wknd day)  
 Bin 5a - 3 valid days (missing wk day and wknd day)  
 Bin 5b - 3 valid days (missing 2 wk days)  
 Bin 5c - 3 valid days (missing 2 wknd days)  
 Bin 6 - < 3 valid days

**Figure A2.** Bin system used to sort accelerometer data by number of valid weekdays and weekend days for Hartley Bay and Kitkatla.

f) Scripting

The on and off times were then transferred onto the raw .dat files which were entered into KineSoft. At the very top of the dat files, age and on and off times were

entered according to the following format, where 'nmd' represents a non-monitored day:

Age 12  
d1:off time d2:on time  
d2:off time d3:on time  
d3:off time d4:nmd (insert earliest time this week)  
d4:nmd (insert latest time this week) d5:on time  
d5:off time d6:on time  
d6:off time d6:235830

g) Determining moderate to vigorous intensity physical activity cut-offs

The Freedson *et al.* (2005) equation was used in this study because 1) Esliger *et al.* (2005) recommend that age-specific regressions be used until further research is done to provide more robust procedures for adjusting for body size, and because 2) we found that in overweight and obese children and adolescents, the Trost *et al.* (1998) weigh-specific equation reduced MVPA cut-offs to physiologically impossible levels; so much so that in very obese participants, ActiGraph counts corresponding to the lower MVPA thresholds were negative.

## Appendix 5:

### Action Schools! BC Physical Activity Log

ACTION SCHOOLS! BC PHYSICAL ACTIVITY LOG – September 2007

Name: \_\_\_\_\_ School: \_\_\_\_\_ Grade : \_\_\_\_\_

**Directions:**

- 1) Please have your child wear the motion sensor under their clothing.
- 2) The motion sensor should be fitted snugly on the waist with the sensor positioned in the front above the hip. The belt should feel comfortable but not floppy.
- 3) The motion sensor should be worn all day and should only be removed during the day if the child is going swimming, having a bath or a shower. It is not waterproof.
- 4) Please note the time when the motion sensor is first put on the child and when it is taken off daily on the log on the reverse side of this form as well as anything that affected your child's movement patterns on any given day.
- 5) The motion sensor is like a smart 'pedometer' but it is very valuable. Please have your child put on the motion sensor on Monday morning to take it into school and an ASI BC researcher will collect them from the classroom.

Thank you very much for you help!

	Tues	Wed	Thurs	Fri	Sat
Dates					
On Time AM					
Off Time PM					
Did weather change your routine?	No	No	No	No	No
	Yes	Yes	Yes	Yes	Yes
Did illness change your routine?	No	No	No	No	No
	Yes	Yes	Yes	Yes	Yes
Was motion sensor removed during wear time?	No	No	No	No	No
	Yes	Yes	Yes	Yes	Yes
If yes, what time?	__ : __ to __ : __	__ : __ to __ : __	__ : __ to __ : __	__ : __ to __ : __	__ : __ to __ : __
Any problems? Please explain.					

**Appendix 6:****Food Frequency Questionnaire (sample page)**

7. Over the last week, how often did you drink a **100% fruit juice** or **100% fruit juice mixtures** (such as apple, grape, pineapple, or others)?

- |  |   |
|--|---|
| <input type="radio"/> Never (GO TO QUESTION 8) | <input type="radio"/> 1 time per day        |
| <input type="radio"/> 1-2 times per week       | <input type="radio"/> 2-3 times per day     |
| <input type="radio"/> 3-4 times per week       | <input type="radio"/> 4-5 times per day     |
| <input type="radio"/> 5-6 times per week       | <input type="radio"/> 6 or more times a day |

7a. Each time you drank **100% fruit juice** or **fruit juice mixtures**, how much did you usually drink?

- ½ cup (125 ml)
- Mini can (210 mL)
- 1 cup ( 250 mL)
- 1 can (351 mL)
- 1 bottle (587 mL)
- Other

8. Over the last week, how often did you drink **other fruit drinks** (such as cranberry cocktail, fruit punch, lemonade or Kool-Aid, Gatorade, Sunny Delight, diet or regular)?

- |  |   |
|--|---|
| <input type="radio"/> Never              | <input type="radio"/> 1 time per day        |
| <input type="radio"/> 1-2 times per week | <input type="radio"/> 2-3 times per day     |
| <input type="radio"/> 3-4 times per week | <input type="radio"/> 4-5 times per day     |
| <input type="radio"/> 5-6 times per week | <input type="radio"/> 6 or more times a day |

8a. Each time you drank **fruit drinks**, how much did you usually drink?

- ½ cup (125 ml)
- Mini can (210 mL)
- 1 cup ( 250 mL)
- 1 can (351 mL)
- 1 bottle (587 mL)
- Other



## Appendix 8:

Table A1. Characteristics of school-aged First Nations youth.

<i>Variable</i>	<i>All</i>	<i>Incomplete data subsample</i>	<i>Complete data subsample</i>
N	74	35	39
Age (y)	12.45 ± 2.4	13.20 ± 2.5	11.8 ± 2.2*
Pubertal status (pre-/pubertal)	n/a	n/a	24/15
Gender (m/f)	34/40	18/17	16/23
<i>Anthropometrics</i>			
Weight (kg)	55.7 ± 18.7	61.0 ± 19.5	51.0 ± 16.9*
Height (m)	1.53 ± 0.14	1.57 ± 0.15	1.49 ± 0.12*
BMI (kg/m <sup>2</sup> )	23.32 ± 5.38	24.31 ± 5.89	22.43 ± 4.78
z-BMI	1.44 ± 1.11	1.52 ± 1.16	1.37 ± 1.07
Waist circum. (cm)	75.49 ± 14.08	78.21 ± 15.26	73.04 ± 12.63
Hip circum. (cm)	88.71 ± 12.75	92.10 ± 12.16	85.67 ± 12.65*
% Overweight	51.4	54.3	48.7
<i>Insulin resistance</i>			
Fasting insulin (pmol·L <sup>-1</sup> )	n/a	n/a	52.15 ± 35.27
HOMA-IR	n/a	n/a	1.79 ± 1.27
<i>Diet</i>			
Energy intake (kcal·d <sup>-1</sup> )	1855.63 ± 746.32	1840.83 ± 715.43	1868.83 ± 782.10
<i>Physical activity variables</i>			
Mean physical activity intensity (counts·min <sup>-1</sup> )	714.7 ± 214.2	733.2 ± 236.1	707.1 ± 207.3
MVPA (min·d <sup>-1</sup> )	135.4 ± 35.41	125.8 ± 38.8	139.34 ± 34.36
Sedentary (min·d <sup>-1</sup> )	445.98 ± 65.18	458.58 ± 70.51	441.25 ± 63.35*
VO <sub>2</sub> max <sub>pred</sub> (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	40.95 ± 6.15	40.0 ± 7.06	41.76 ± 5.23
Mean wear time (h·d <sup>-1</sup> )	12.7	12.7	12.7
Mean valid days	4.4	4.2	4.4

Data are ratios, percentages or means ± sd. \*p<.05 for difference between the incomplete and complete data subsamples (t-test).

### Appendix 9:

**Table A2.** Prevalence of insulin resistance, hyperinsulinemia and impaired fasting glucose using different thresholds for HOMA-IR, fasting insulin and fasting glucose.

Subgroups	<i>HOMA-IR</i> ≥ 2.10	<i>HOMA-IR</i> ≥ 2.28	<i>HOMA-IR</i> ≥ 3.16	<i>FI</i> ≥ 137.6 <i>pmol·L<sup>-1</sup></i>	<i>FG</i> ≥ 5.6 <i>mmol·L<sup>-1</sup></i>	<i>FG</i> ≥ 6.1 <i>mmol·L<sup>-1</sup></i>
<b>All</b> (n=39)	12 (30.7%)	10 (25.6%)	4 (10.3%)	2 (5.1%)	7 (18%)	1 (2.6%)
<b>Pubertal Status</b>						
<i>Pre-</i> (n=24)	5 (20.8%)	3 (12.5%)	0 (0%)	0 (0%)	5 (20.8%)	0 (0%)
<i>Puber.</i> (n=15)	8 (53%)	7 (46.6%)	4 (26.7%)	2 (13.3%)	2 (13.3%)	1 (6.7%)
<b>Gender</b>						
<i>Male</i> (n=16)	6 (37.5%)	4 (25%)	1 (6.3%)	0 (0%)	5 (31.3%)	1 (6.3%)
<i>Female</i> (n=23)	7 (30.4%)	6 (26%)	3 (13%)	2 (8.7%)	2 (8.7%)	0 (0%)
<b>Weight Status</b>						
<i>Non-overweight</i> (n=20)	4 (20%)	2 (10%)	1(5%)	0 (0%)	3 (15%)	1 (5%)
<i>Overweight</i> (n=10)	2 (20%)	3 (30%)	1 (10%)	1 (10%)	2 (20%)	0 (0%)
<i>Obese</i> (n=9)	6 (66.7%)	5 (55%)	2 (22.2%)	1 (11.1%)	2(22.2%)	0 (0%)

FG, fasting glucose; FI, fasting insulin

**Appendix 10:****Table A3.** Summary table illustrating the differences in means between the subgroups ( $p < .05$ ).

	<b>Subgroups</b>			
	<i>Gender</i>	<i>Pubertal status</i>	<i>Weight status</i>	<i>Physical activity level</i>
<i>Average PA</i>	B>G			
<i>MVPA</i>	B>G			
<i>Stage</i>	B>G			HPA>LPA
<i>Waist Circ.</i>		Pre<Puber		
<i>F&amp;V</i>	B<G		N>O	
<i>SSB</i>	B>G			
<i>Fasting Insulin</i>		Pre<Puber	N<O	HPA<LPA
<i>HOMA-IR</i>		Pre<Puber	N<O	HPA<LPA

B = boys, G = girls, Pre = pre-pubertal, Puber = pubertal, N = normal weight, O = overweight, HPA = high physical activity and LPA = low physical activity. Stage = Stage achieved on Leger-Boucher aerobic test; F&V = Fruit and vegetable intake as determined by the 24hr Recall Questionnaire; SSB = Sugar sweetened beverage intake as determined by the Food Frequency Questionnaire.

**Appendix 11:**

**Figure A3.** Multiple regression model predicting HOMA-IR values for a pre-pubertal and overweight First Nations child engaging in 90 versus 120 minutes of MVPA per day (pre-pubertal = 0, pubertal = 1; MVPA in min·day<sup>-1</sup>).

$$\log \text{HOMA-IR} = 0.171(\text{Pubertal status}) + 0.076(\text{zBMI}) - .003(\text{MVPA}) + 0.351$$

$$\log \text{HOMA-IR} = 0.171(0) + 0.076(1.43) - .003(\mathbf{90 \text{ vs } 120}) + 0.351$$

$$\log \text{HOMA-IR} = 0.18968 \text{ vs } 0.09968$$

$$\text{HOMA-IR} = \mathbf{1.55 \text{ vs } 1.26}$$

Therefore, the difference in predicted HOMA-IR values for a pre-pubertal and overweight First Nations child engaging in 90 versus 120 minutes of daily moderate to vigorous physical activity is 0.29, or 23%.

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