Is the change in Body Mass Index among youth newly diagnosed with type 1 diabetes mellitus associated with obesity at age 18?

by

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Abstract

Background: Patients diagnosed with Type 1 diabetes mellitus (T1DM) require insulin therapy. Although necessary, insulin therapy is associated with an immediate increase in Body Mass Index (BMI). Excessive increase in BMI may lead to obesity, which is associated with both short and long-term negative health outcomes. The objective of this study was to determine whether weight change in the six months after diagnosis in children and adolescents with T1DM is related to obesity status at age 18.

Methods: Data from the Diabetes Education Resource for Children and Adolescents database was used for this study. This unique database combines extensive clinical information on each patient with virtually universal coverage. The study population comprised all children 2-18 years old diagnosed with T1DM by DER-CA endocrinologists in Manitoba between 1997 and 2012 (N=377). BMI z- scores calculated from measured height and weight were used to classify BMI group membership using the 2000 Centers for Disease Control growth charts. Regression models were used to assess the association between change in BMI z-score six months after diagnosis, and BMI z-score at last visit prior to transfer to adult care. The models controlled for BMI z-score at diagnosis, sex, pubertal status and length of follow up. Additional stratified analyses examined sub-groups within the sample, to determine whether the effects were different for children with different characteristics (e.g. sex and pubertal status at diagnosis).

Results: At diagnosis, 9% of the study cohort was underweight, 68% normal weight, 15% overweight and 8% obese. Most, (91%) but not all patients gained weight in the six months after T1DM diagnosis and initiation of insulin therapy. The pattern of weight change differed by BMI group at diagnosis, sex, and pubertal status. At last visit, average BMI z-scores for all groups of patients were above zero, and varied less than BMI z-scores at diagnosis. Results of the multivariate analytic model (adjusted R^2= 0.56) show that BMI z-score at diagnosis was most important, followed by female sex, change in BMI z-score in the six months after diagnosis, the interaction between BMI z-score at diagnosis and change in BMI z-score in the six months after diagnosis, and duration of follow up.

Conclusion: Results of this study demonstrate that patients' BMI group, sex, and pubertal status at diagnosis influenced the pattern of their BMI z-score change in the six months after diagnosis, and thereafter. Diabetic care teams may need to monitor not only the amount of weight change in the period after T1DM diagnosis, but also consider BMI at diagnosis.

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Chapter 1: Introduction and study objectives

1.1 Introduction

Diabetes mellitus (DM) is a chronic disease affecting people of all ages with a potential to cause serious complications[1]. It is a metabolic disease characterised by high blood glucose (hyperglycemia) due to defective insulin secretion, defective insulin action or both[1]. The majority of DM cases are either type 1 diabetes mellitus (T1DM) or type 2 (T2DM)[2]. T1DM occurs when the pancreas fails to produce insulin due to the autoimmune destruction of beta cells in the pancreas[3] and T2DM mostly results from insulin resistance or insulin secretory defects[4]. The International Diabetes Federation reported that in 2013, approximately 382 million people were affected by DM worldwide[5].

In Canada, an estimated 2.4 million people were living with DM in 2008/9 [6,7], and the number is expected to grow to 3.7 million by the year 2019[7]. T2DM constitutes 90-95% of all cases, but T1DM is the most common type of youth-onset DM[6]. Previous studies have shown that the incidence of T1DM has been rising in many countries over the past few decades[8-12], especially in children under the age of five[13]. However, results from recent European studies suggest that the trends may have levelled off[14-16].

Contrary to the conventional belief that most T1DM patients are underweight or in the normal weight category at disease onset, some studies[17,18] have shown that young children diagnosed with T1DM have a BMI z-score equal to or greater than children from the general population

of children. Other studies have shown that young children who developed T1DM were heavier than controls during their pre-diabetes period[19,20]. Weight gain in infancy and early childhood as a risk factor for T1DM has been described previously[21] and is further supported by proponents of the disputed and controversial "accelerator hypothesis" which argues that T1DM and T2DM are one and the same but only distinguishable by the rate of pancreatic beta cell loss[22].

The increasing incidence and prevalence of T1DM is concerning because prolonged hyperglycemia is associated with complications such as cardio-vascular disease[23], nephropathy[24], vascular damage[25], neuropathy[26], retinopathy[26,27], and periodontal disease[28]. These complications are associated with morbidity and premature mortality. According to the Canadian Diabetes Association, poorly managed T1DM can shorten life expectancy by as much as 15 years[29]. However, changes in diabetes care over time have led to improved survival[30,31]. Furthermore, in 2010 the Canadian Diabetes Association estimated that the economic burden of diabetes in Canada was $12.2 billion, and is expected to rise as disease prevalence increases[3].

The recommended management of T1DM includes regular administration of insulin to maintain optimal glycemic control[32-34]. While essential for controlling blood glucose levels, insulin therapy is associated with hypoglycemia and excess weight gain, especially soon after its initiation[35,36]. Intensive insulin therapy, which is associated with increased risk of weight gain[37], may be required to counter insulin resistance which has been reported in females and children

with higher than normal BMI[38]. Acute changes in weight after T1DM diagnosis have been attributed to rehydration[36,39], replenishment of lost fat and lean body mass, changes in eating habits, and possibly the anabolic effect of insulin on lean and fat tissue[40]. Fear of hypoglycemia has been linked to compensatory overeating[41] and physical in-activity[42] which are both known to cause an increase in BMI.

1.2 Statement of the problem

Results from several studies have shown that children and adolescents with T1DM gain weight immediately after diagnosis[35,36,40]. Excess weight gain can lead to overweight or obesity which is known to track from childhood to adolescence and into adulthood[43-45]. Obesity has been linked to numerous chronic diseases, morbidity and premature mortality[46]. Childhood and adolescent overweight and obesity have risen significantly over the past few decades[47]. T1DM patients gaining excess weight while on insulin may be at higher risk of becoming overweight or obese adults.

The potential burden posed by the concurrent problems of obesity and T1DM may have significant consequences for patients, and their families[48]. Although weight gain in children and adolescents diagnosed with T1DM has been well documented after starting insulin therapy, there have not been any published studies describing its long-term consequences[35,36]. Such findings may be helpful for informing clinical practice and diabetic education in this patient population.

1.3 Study objective(s)

The objectives of this study were:

1. To document the prevalence of underweight, normal weight, overweight, and obesity in a cohort of youth diagnosed with T1DM in Manitoba.
2. To assess and describe patterns of change in weight (BMI z-score) in the six months after diagnosis with T1DM.
3. To examine if the change in BMI (z-score) within six months of diagnosis of T1DM in children and youth is associated with obesity at age 18.

1.4 Hypotheses

1. After controlling for other factors, a change in Body Mass Index (BMI) in the 6 months after diagnosis of T1DM is not associated with obesity at age 18.
2. The pattern and magnitude of weight change after diagnosis is similar among all children and adolescents with T1DM.

1.5 Assumptions

The key assumptions for this study include:

1. BMI z-score is a valid measurement of adiposity in children and adolescents.
2. The BMI z-score for the study population are normally distributed.
3. The 2000 Centres for Disease Control (CDC) growth charts provide valid reference data for assessing BMI group membership among Canadian children and adolescents diagnosed with T1DM.

Chapter two: Literature review

2.1 Epidemiology of youth onset T1DM

Several[49-52], but not all[53-56], population-based registries show an increasing incidence of youth onset T1DM over time[57]. Lack of accurate data, insufficient reporting and geographical variations in reported estimates make accurate analysis of global incidence of youth onset T1DM challenging[50,58]. Large epidemiologic studies reporting on data from the 1980s onwards indicate that the global incidence of T1DM has been increasing by 2% to 5% annually[59-61]. In particular, the increase in the incidence of T1DM in the very young (0-4 years) has been reported in Europe and North America in recent decades[57,64]. However, results from recent European studies, suggest that this trend may be levelling off[14-16]. Onset of T1DM is typically before 20 years of age, with a peak incidence between the ages of 10 and 14[58,60,62], but it can also occur later in life[63].

2.2 Incidence of T1DM

Generally defined as the number of new health-related events in a defined population within a specified period of time, disease incidence can be measured as a frequency rate, count or a proportion[65]. A key report by the International Federation of Diabetes estimated that there were 79,100 new cases of T1DM among children between the ages of 0-14 years in 2013 alone[5]. Average annual age-standardized incidence rates in Europe between 1989 and 2003 ranged from 4.7 per 100, 000 in Romania to 39.9 per 100,000 in Finland[59]. In the United States of America, overall annual incidence of T1DM among children 0-10 years was estimated to be 19.7 and 18.6 per 100,000 among 10- 19 years between 2002 and 2005[66].

In Canada, accurate estimates of the incidence of T1DM among children and adolescents are not available[6,7]. However a 2009 report by the International Diabetes Federation , used reports from provincial estimates and reported that the incidence of TIDM among 0-14 year old Canadian children was 21.7 per 100,000[67]. A report from Newfoundland and Labrador, estimated a T1DM incidence rate of 49.9 per 100,000 per year among 0-14 year olds[68]. An earlier study from Manitoba in 1997 based on data collected between 1985 and 1995, reported an annual incidence of 20.4 per 100,000 among 0-14 year old children[69]. Diabetes Education Resources for Children and Adolescents (DER-CA)'s 2012 annual report provides the most recent and accurate incidence of TIDM among children and adolescents in Manitoba[70]. Between 2008 and 2012, there were 300 new cases of youth onset T1DM in Manitoba with an average of 60 new cases per year[70]. Based on these statistics, the annual incidence of TIDM in Manitoba for this period was 15.53 per 100,000.

2.3 Prevalence of T1DM

Prevalence is the measure of occurrence or disease frequency, often used to refer to the proportion of individuals in a population at a particular time or period who have a disease or condition[65,71]. It is a proportion whose types include annual, point and period prevalence[65]. The few studies that have examined the global prevalence of T1DM among children and adolescents show that the prevalence of T1DM is increasing[58,59]. In 2011, it was estimated that 490,000 children younger than 15 years had T1DM worldwide[58]. Prevalence of T1DM among European children 0-15 years of age is predicted to rise from 94,000 in 2005, to 160,000 in 2020[59]. In the USA, it was estimated that in 2001 the prevalence of T1DM among youth (<20 years) was 1.54 per 1000[72].

Accurate estimates among Canadian children are not available[6], although in a 1997 study, Blanchard and associates reported a point prevalence of 1.24 per 1000 among children in Manitoba[69]. Dart (2010), reported a 1.57 per 1000 prevalence estimate for youth onset T1DM in Manitoba[73]. DERCA's 2012 annual report provides the most recent prevalence estimates for youth onset T1DM in Manitoba[70]. On average, there were 505 cases of T1DM in Manitoba during the period 2008-2012 representing annual prevalence of 1.31 per 1000.

2.4 Pathophysiology

T1DM is a chronic disease that results from autoimmune destruction of the insulin-producing Beta cells in the pancreas[6,74,75], usually leading to absolute insulin deficiency[1]. The clinical onset of T1DM is preceded by the appearance of autoantibodies against beta cell antigens[76]. This immune response may produce secondary and tertiary immune responses that contribute to the impairment of beta cell function and destruction[75].

Once beta-cell function is impaired, the resulting lack of insulin, a hormone that is central to the metabolism of carbohydrates and fats[74,77], leads to excessively high blood glucose levels, along with a potential for other deleterious health outcomes including micro and macrovascular complications[9,78]. A number of hypotheses have linked environmental risk factors (due to seasonal variations in incident cases), diet, viral infections, and genetic predisposition to T1DM[64,74,79,80].

2.5 Diagnosis

T1DM often present with unexplained weight loss, increased volume of urine (polyuria), and increased thirst (polydipsia)[81,82]. Additionally, high levels of sugar in the urine (glycosuria),

excessive hunger (polyphagia), inability to control urine (enuresis), hyperglycemia, generalized body malaise and diabetic ketoacidosis (DKA) may be present at diagnosis[4,81,83]. The diagnostic criteria for T1DM is based on thresholds of glycaemia and diagnosis is made on the basis of a fasting plasma glucose (FPG) ≥ 7.0 mmol/L; or casual plasma glucose (CPG) ≥ 11.1 mmol/L in addition to symptoms of diabetes[1,82]. Individuals presenting with typical symptoms of T1DM should initiate insulin therapy without delay, however those who present with no symptoms but suspected to have T1DM, should have a repeat test on a second day to confirm the diagnosis[82].

2.6 Complications and consequences of T1DM

Youth onset T1DM is associated with both short term and long term complications[84,85]. Acute complications such as DKA and severe hypoglycaemia have been known to cause morbidity and mortality[82,86]. DKA is a potentially life threatening acute complication of T1DM which is characterized by a biochemical triad of hyperglycemia, abnormally high amounts of ketones in the urine (ketonuria) and low blood pH (acidemia)[87]. DKA is caused by a decrease in effective circulating insulin associated with elevations in counter-regulatory hormones[88]. Delays in the diagnosis of T1DM and omission of insulin are the major causes of DKA in children and adolescents[87]. A previous study reported that participants who presented in DKA at diagnosis had lower BMI than those without DKA although the differences were not statistically significant[35]. At the other end of the spectrum is another potential complication, hypoglycaemia which can be caused by inadequate caloric intake, excessive insulin dosage or inadequate preparation for physical activity but often the cause cannot be determined[84]. Fear

of hypoglycemia may interfere with an individual's ability to achieve optimal glycemic targets[84], while a severe episode can predispose the individual to further episodes[89].

As the disease process progresses, microvascular and macrovascular complications become dominant and more concerning[86,90]. Micro-vascular complications of T1DM are characterised by damage to the kidneys, retina, and neurons[91]. The presence of microvascular complications as well as hypertension, and dyslipidemia are risk factors for future macrovascular complications[92]. The most common macrovascular complications of T1DM include cardiovascular disease, stroke and peripheral artery disease[84,85,92]. T1DM complications have also been linked to poor quality of life[93,94], and premature mortality [91].

2.7 Management of T1DM

2.7.1 Insulin therapy

The main priority in managing T1DM is to achieve optimal blood glucose levels: known to delay the onset or prevent both micro and macrovascular complications of diabetes[1,95-97]. Near-normal blood glucose levels can be achieved by regular administration of insulin, the mainstay in medical management of T1DM[1,82]. Insulin therapy aims to mimic the natural pattern of insulin secretion by the pancreas as closely as possible to maintain stable blood glucose levels[42,98]. The choice of insulin regime depends on many factors, including the child's age, duration of diabetes, family lifestyle, socioeconomic factors, and family, patient, and physician preferences[1,82].

Soon after diagnosis, a patient may achieve optimal glycemic control with modest insulin dosage (a time often referred to as the honeymoon period). After this initial period of varying duration, intensive insulin may be required to maintain better glycemic control[1]. Intensive insulin therapy (IIT) or Flexible Insulin Therapy (FIT) delivered as insulin analogues attempts to simulate physiological insulin needs more closely, providing independently both basal insulin and meal insulin requirements and allows for rapid adjustment of each component[97]. Insulin analogues were introduced as part of standard clinical practice in 2001 and may affect the pattern and trajectory of weight change among children with T1DM in a way that differs from those using regular insulin which was the standard of care practice prior to the introduction of analogues[99]. The long acting insulin analogue detemir has been reported to cause less weight gain than other insulin regimens[100]. While it is recommended and known to achieve better glycemic control[101], intensive insulin therapy in patients with T1DM is also associated with significant weight gain especially in the period immediately after its initiation[102,103].

2.7.2 Diabetes education

Dealing with the diagnosis of a life-long condition such as T1DM with requirements of multiple daily injections, regular monitoring, and risk of complications, can be daunting for the patient and their family[42]. Carefully planned and empathetic education is therefore important in the period soon after diagnosis and thereafter[104]. Evidence from previous studies suggests that education about the disease, glucose monitoring, complications, and insulin regimens, how to self-manage diet and the expected challenges to the patient and their family is associated with reduced hospitalizations, emergency room visits, and overall costs[105]. Ideally, a team of professionals including a physician, nurse, dietician, physical activity/exercise specialist and a

mental health professional will comprise the diabetic education team for children and adolescents[82,106]. Education should be developmentally and age appropriate, culturally sensitive and individualized to the needs of each patient and their family[82,107].

2.7.3 Diet

Nutrition management is an important aspect of diabetes care but there is little scientific evidence to support specific diabetic diets[41]. The Canadian Diabetes Association Clinical Practice Guidelines[1] as well as other key reports recommends that children with diabetes should follow the same healthy diet as all other children without diabetes[41,108,109]. Although they endorse the regular healthy diet approach, an international report emphasised the need for more research into diet requirements for youth with T1DM[41]. On the other hand, the American Diabetes Association wrote a position statement recommending Medical Nutrition Therapy (MNT)[110]. They advocate maintenance of a balance between carbohydrate intake and insulin levels to achieve near-normal blood glucose levels[110]. Furthermore, the recommendations seek to reduce the risk of youth overweight and diabetes-related co morbidities, including dyslipidemia and cardiovascular disease. Silverstein and associates, posit that this can be accomplished through individualized meal planning, flexible insulin regimens and algorithms, self-monitoring of blood glucose (SMBG), and education promoting decision-making based on documentation and review of previous results[82]. Additionally, consultation with a pediatric dietician with experience in managing diabetes is often recommended for counselling and MNT[41,82,108]. A primary component of medical nutrition therapy in T1DM is the development of individualized meal plans that integrate insulin regimen and carbohydrate estimation into the family's

lifestyle, conforming to preferred meal routines, food choices, and physical activity patterns[41,109].

2.7.4 Exercise

Exercise, a subset of physical activity that is characterized by planned and purposeful training[111], is increasingly considered a critical component of a healthy, balanced lifestyle, which helps to prevent, delay, or limit some common chronic diseases[112]. Regular physical activity is recommended for optimal management of T1DM[1,113] because it is associated with improvement in insulin sensitivity, controlling BMI and lipid profiles; boost self-confidence; improve psychological health and most importantly, optimize long-term protection against cardiovascular disease[90,114]. While regular exercise is recommended and now integral in the management of T1DM, there is a risk of exercise-induced hypoglycemia fear which is a constant threat to adherence for patients with diabetes[90,115]. To prevent or reduce episodes of hypoglycemia, T1DM patients must ensure adequate carbohydrate intake before and after physical activity. Patients may also reduce the doses of their regular and rapid acting insulin and frequently self-monitor their blood glucose[116]. In some cases, the fear of exercise-induced hypoglycemia results in compensatory overeating[41,117], and/-or reduced participation in physical activity which are both independently associated with weight gain[42].

2.8 Previous studies on insulin-induced weight gain in youth diagnosed with T1DM

A number of studies have examined BMI changes in children and youth with T1DM. Domargard et al examined changes in height and weight among a group of children and adolescents (2-17 years old), with T1DM (n=89) transferring from pediatric to adult care, and compared it to a similar sized control group of sex and age matched youth without T1DM[118]. They obtained

longitudinal measurement data on 85% of the children with diabetes from diagnosis to the age of 18. A school nurse randomly recruited a control group of 89 adolescents whose height and weight measurements were obtained at the school. Both groups were further subdivided into pre and post-pubertal using age at maximal growth velocity which occurred at 11 for females and 13 for males. Data collected yearly for patients with pre-pubertal onset of T1DM (N=50) was retrospectively analysed up to the age of 18. Prospective longitudinal data were also obtained for 65 participants between the ages of 18-22. A Stadiometer was used to measure height at the age of 18 and during follow up and BMI was calculated as weight/ (height^2).

At 18, females with T1DM had a higher BMI than the controls: 33% of females with T1DM versus 4.3% of controls had a BMI above the 90th percentile. T1DM females had mean weight 6.5 kilograms higher than controls at 18. Between ages 18 and 22, females without T1DM had a significant (3.2 kilograms) weight increase compared to only 1.6 kilograms for those with T1DM. There were no significant differences in weight increases between T1DM males and controls at 18 or during follow up between the ages of 18 and 22. Only 8% of the 18 year old males with diabetes had a BMI above the 90st percentile for age. Domargard and associates noted that while the sex difference in weight development could not be explained by their results, they speculated that hormonal differences may have contributed to the differences observed given that most of the weight-gain was observed in females after menarche[118].

Results from this study provide insights on weight gain in youth diagnosed with T1DM but important methodological shortcomings need to be noted. Although the study reports that

reliable measurement data from diagnosis to age 18 were obtained, neither their source nor collection methods are described in the study. For example, the equipment and processes used for weight measurement were not specified. The trajectory of weight gain in the period immediately after diagnosis and initiation of insulin was not reported, despite evidence in the literature showing that rapid weight gain in this population occurs during this period[35,36]. Failure to describe recruitment of the controls raises concerns about their representativeness.

Newfield et al examined longitudinal changes in weight and BMI in the period after T1DM diagnosis (≈7 months)[35]. They retrospectively obtained data for 136 subjects (0-18 years of age), who were admitted at the time of diagnosis. The average age at diagnosis was 9 ± 4.5 (mean ± SD) and 44% of the study participants were female. The average BMI z-score at diagnosis was -0.23 with no statistically significant sex or age differences: 14.6% of participants were overweight and 7.7% were obese.

Results showed a rapid increase in weight and BMI z-score, with significant differences by as early as two weeks post diagnosis. BMI z-score reached plateau at 10 weeks, with the mean BMI z-score of 0.86. There was no statistically significant difference in BMI z-score or percentage of weight change by sex, age or pubertal stage. Participants who presented in diabetic ketoacidosis at diagnosis tended to have a lower BMI z-score (-0.6) than those without DKA (-0.18). Varying post diagnosis visit intervals, and the retrospective nature of the data presented were noted as limitations in this study[35]. While rates of overweight and obesity at

diagnosis were noted, the prevalence of underweight was not reported although literature suggests that loss of weight is a classic presentation in T1DM.

Davis et al evaluated body composition changes after diagnosis of T1DM and markers of cardiovascular risk[36]. Thirty subjects between the ages of 0-18, who were within 1 week of T1DM diagnosis and fourteen controls were prospectively recruited. The controls were age and sex matched, recruited from friends and siblings of the subjects and had measurements on two occasions one year apart. There were no height differences between subjects and controls at diagnosis or 1 year later. At diagnosis, T1DM patients had significantly lower BMI z-score (-0.67) than the controls (0.20), and reduced percentage body fat: 20.3% vs. 24.5%, but after 6 weeks of insulin therapy, those differences were no longer significant. Females with diabetes had a significantly lower BMI z-score (-1.64) than males (-0.02) at diagnosis and at 1 year post diagnosis. Females with T1DM had a significantly higher HbA1c compared to males despite receiving a higher insulin dose/kg body. Davis and associates attributed the females' higher HbA1c at 1 year after diagnosis to increased insulin resistance among the females. HbA1c at diagnosis was correlated with the post-diagnosis increase of body fat in grams ($r=0.60$, $p<0.05$) and BMI z-score ($r=0.57$, $p<0.05$)[36].

This study was limited by the small number of controls. Long term consequences of insulin therapy on body composition were not explored past 1 year from diagnosis. This potentially limits the validity of inferences that can be made from the study about true cardiovascular risk given the length of time that it may take from exposure to risk manifestation.

de Vries and associates assessed the patterns of weight gain and BMI changes following T1DM diagnosis in pediatric patients and identified factors associated with a higher BMI[40]. The cohort was comprised of 209 patients (0- 18 years old; mean age 9.2 ± 4.3), were diagnosed with T1DM between 2000 and 2004 and followed regularly for 6 years. They excluded participants with any condition or on medications that are known to independently affect weight gain. Measurement data collected ≥ 1 year(s) prior to diagnosis, at a community clinic were available for 64% of the participants. Weight standard deviation scores (Wt-SDS), height standard deviation scores (Ht-SDS), BMI, and BMI z-score were calculated for participants, their parents and siblings. Overweight and obesity rates; defined using the National Center for Chronic Disease Prevention and Health Promotion[119] criteria, were calculated 6 years post diagnosis and compared to the USA National Survey for 7th and 12th grade children.

For T1DM patients, their BMI-SDS at diagnosis was significantly lower than pre-diagnosis, but rapidly increased predominantly in the first 2 weeks and peaking at 3 months post diagnosis. At their peak, BMI-SDS and Wt-SDS were found to found to be significantly higher than pre-diabetes onset. Although the weight and BMI changes stabilized between 6-12 months post-diagnosis, at 6 years follow up, the BMI-SDS were significantly higher than at 6 months after diagnosis[40]. Unlike the study by Davis et al[36], de Vries and associates found that the BMI z-score for males and females at diagnosis were similar, and declined to a nadir at 6 months for females and 12 months for males[40]. Increases in BMI z-score between 3-6 years was only observed in females and at the 6 year follow up, females had a significantly higher BMI z-score than their

male counterparts. Comparisons between the patients and National Survey results for same ages indicated that overweight but not obesity was significantly higher among participants.

Another study by Sandhu and associates examined the prevalence of overweight and obesity in children and adolescents with T1DM and compared this to a control group consisting of 565 children of the same age group[48]. They conducted a retrospective review of medical charts for 390 children with T1DM between the ages of 6 and 16 years. Children with other endocrinopathies such as type 2 diabetes, cystic fibrosis and celiac disease were excluded from the study. Age, sex, date of diagnosis, weight and height were collected. The children were divided into pre-pubertal (6-9.99 years), pubertal (10-13.99 years) and post-pubertal (14-15.99 years). The Centers for Disease Control (CDC)'s growth charts were used to define overweight and obese status, and BMI values were converted to BMI-z score[119,121,122]. At baseline, there was a statistically significant difference in mean age between the T1DM and control groups[48].

Sandhu and associates found a significantly higher prevalence of overweight but not obesity among the T1DM group compared to the controls[48]. The higher prevalence of overweight among T1DM patients increased with age and was more marked in females. Their finding is similar to that by de Vries and others who also found the prevalence of overweight but not obesity among T1DM patients to be higher than the controls.

In a recent multi-centre observational study, Frohlich-Reiterer et al evaluated the predictors for increasing BMI in children and adolescents with T1DM (n= 12,774) during the course of the

disease[123]. They included patients diagnosed with T1DM for more than 6 months, documented BMI at T1DM onset, negative antibody screening for celiac disease, and documented BMI and insulin therapy during follow up. Patients were put into groups based on diabetes duration and age groups. BMI z-score were used and weight status classification was based on national criteria established for children and adolescents in Germany. They applied linear mixed longitudinal regression models using a repeated measurement design to assess predictors of weight change during the course of diabetes.

Female sex, age at T1DM onset, low BMI at diabetes onset, intensified insulin therapy and higher insulin dose, pubertal diabetes onset, and long diabetes duration were significant predictors of weight gain in children and adolescents during the course of diabetes. This multi-centre observational study was limited by lack of data on daily caloric intake of patients, and physical activity levels which can independently affect BMI[123].

2.9 Overweight and obesity

Obesity is generally defined as the abnormal or excessive accumulation of fat in adipose tissue to the extent that health may be impaired[124]. Power and associates suggested that an ideal measure of body fat should be accurate in its estimate of body fat; precise, with small measurement error; accessible, in terms of simplicity, cost and ease of use; acceptable to the subject; and well documented, with published reference values[125]. None of the current measures of body fat satisfies the above criteria[126]. Direct measurement of body fat is preferable to indirect measurement but it is not used frequently because of inaccessibility and other shortcomings[126,127].

Ideally, direct measurement of body fat would be done by methods such as underwater weighing, dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) and computed tomography (CT)[126,128]. However, these methods are very costly and therefore not easily accessible and are not used in daily practice[128]. For this reason, obesity is often assessed by indirect estimates of body fat[129]. In large-scale population surveys and clinical/public health screening, an index of body weight adjusted for stature is commonly used as a surrogate for body fat content[128,130]. The most widely used index of relative adiposity is Quetelet's index, better known as body mass index (BMI)[128].

2.10 Overweight and obesity in children and adolescents

Determining weight status and level of adiposity in children and adolescents is more challenging because of rapid growth and physical development with significant changes in height and body composition during this maturation period[128]. Classifying overweight or obesity according to a single measure in children and adolescents is therefore difficult and potentially more susceptible to measurement error[128]. In addition, according to the World Health Organization, "international or regional weight status standards for children and adolescents may be less reliable as the age of onset of puberty and its associated physical changes often varies between different countries, ethnic groups or cultures"[124]. Because of these challenges, where possible, combining results from common anthropometric measures such as skin folds, waist circumference and BMI is often recommended[131]. However, due to resource and time constraints, BMI is the most commonly used method for estimating incidence and prevalence of overweight and obesity in children and adolescents[128].

2.11 Body Mass Index

BMI: (weight (kg) /height squared (m^2)), is the most convenient and practical way of estimating relative adiposity at the population level among children, adolescents and adults[126,132]. It was first developed for use in measuring adiposity in adults[133] but in recent years, several[124,126,134,135] but not all[136,137] studies have recommended its use to estimate childhood and adolescent overweight and/or obesity. Like any other surrogate measure, using BMI to estimate relative adiposity has its own limitations[138,139] especially when used for children and adolescents[140,141]. The accuracy of BMI as a measurement of adiposity relies to some extent on the skills of the measurer[126,142].

Unlike in adults, BMI varies substantially by age and sex during childhood and adolescence[143,144], therefore it needs to be evaluated against age and sex-specific reference values[126,141]. Some studies have also indicated that BMI varies by race and maturation stage[145-147]. Because of the these reasons, BMI values need to be further transformed into a common footing such a z-score or percentile when being used for pediatric populations [141,143]. BMI z-score or percentiles represent a measure of weight adjusted for sex and age[143]. In most cases, BMI z-score will be used to estimate adiposity in children and adolescents relative to local or international reference data or growth charts[142]. However, the main challenge to investigators is to choose the set of growth charts or reference data that is most appropriate for the intended purposes for which the BMI data will be used[142].

2.12 Reference Data for measuring adiposity in children and adolescents

Reliable reference data or growth charts have to be used when BMI z-score are used to estimate adiposity in children and adolescents[142]. Three internationally recognized growth charts (International Obesity Task Force, Centres for Disease Control and World Health Organization), are often used for reference when dealing with children and adolescents. Results from previous studies comparing the three international growth charts have shown different estimates of overweight or obesity status[148,149].

The International Obesity Taskforce (IOTF) sponsored a workshop with a goal of establishing a standard definition for child overweight and obesity worldwide[150]. An international survey of six large nationally representative growth studies was conducted involving close to 200,000 subjects. Centile curves for BMI were constructed for each dataset by sex, and superimposed on each other leading to clusters of centile curves that passed through adult cut-off points at the age of 18[150].

In 2006 and 2007, the WHO created growth charts for children (0-5 years)[151], and thereafter for those 5-19 years of age[152]. These charts were constructed using three datasets with a sample of 30, 000 subjects, which were adjusted for age, and sex. Subjects with biologically implausible height and weight values were excluded from the analyses. Cut-off points were made using standard deviations from the WHO standard median[152]. The growth charts developed by the Centres for Disease Prevention and Control (CDC) in 2000 were used for this study[121]. The CDC growth charts were developed using USA data from nationally representative surveys. These

growth charts were adjusted for age and sex, with cut-offs that correspond to specified percentiles which classify individuals as underweight, normal weight, overweight, and obese[121].

2.13 Epidemiology of childhood overweight and obesity

Several studies[47,152-155] including a key international report from the World Health Organization [156] have described childhood obesity as one of the most serious public health challenges of the early 21st century due to its association with premature mortality[157-160], morbidity[161-163] and the development of non-communicable diseases (NCD) in adulthood[164-166]. Childhood overweight or obesity has complex determinants that include socio-demographic, environmental, psychological, technological, behavioural and biological factors, all operating at individual, family and societal levels[167-170].

Global estimates show a continued rise in prevalence[171,172], although a recent study suggested that rates may have plateaued[173]. Approximately 43 million (7%) children under the age of 5 were estimated to be overweight or obese in 2010[153,174,175]. This represented a 35% increase from 28 million in 1990, and projected to reach a prevalence of 9.9% by 2025 if current trends continue[171]. Prevalence is highest, in high income countries, where in 2011, it was estimated that 15% of school-aged children were overweight[171]. Global overweight and obesity estimates are variable and may over or underestimate prevalence due to numerous and inconsistent measurement methods which are known to yield different results[148,149]. The 2009-2011 Canadian Health Measures Survey[148] identified 19.8% of Canadian children ages 5-17 years as overweight, and another 11.7% as obese[176]. Similarly, a 2007 study in Manitoba found that 22% of children were overweight and 9% were obese[177].

2.14 Childhood overweight or obesity and the risk of T1DM

While most studies have historically documented a positive correlation between childhood obesity and the risk of type 2 diabetes mellitus[178-181], evidence from recent studies suggests an association between childhood obesity and T1DM[21,182,183]. The suggestion that T1DM may be associated with childhood overweight or obesity was first made by Baum and associates in 1975[184], and later re-visited as clinicians and epidemiologists noted the simultaneous rise in the incidence of T1DM and obesity in children[183]. The concept of weight gain as a risk factor for T1DM was further expanded (although contested), by the "accelerator hypothesis"[22] which argues that just like in the case of T2DM, insulin resistance which results from excessive weight gain and physical inactivity is partly responsible for the recent increase in incidence of T1DM[22]. Because secular trends show increasing rates in both obesity and T1DM among children over time[182], year of diagnosis and subsequent initiation of insulin therapy need to considered when evaluating trends of insulin-induced weight in this patient population.

Libman and associates compared the prevalence of overweight in black and white children and adolescents at the onset of T1DM during two time periods (1979-1989 and 1990-1998)[18]. African-American children (N=130) were sex and age matched to an equal number of their white counterparts. Participants were included if they had been assessed by a physician to have insulin-dependent diabetes, below the age of 19, and being treated with insulin therapy at the time of discharge from hospital. Cases of secondary and T2DM diagnosed on the basis of clinical criteria were excluded from study. Demographic and clinical data such as date and age at onset, sex, race, height, weight, family history of diabetes presence of DKA were obtained from

reviewing medical records. Overweight classification was made based on the CDC's 2000 centiles.

The study found a 20 year combined prevalence of overweight and obesity to be 27.5% with no significant sex difference. Overweight obese rates were significantly higher among black participants as was among those with post-pubertal (≥ 11 years) onset of T1DM. Overweight prevalence increased threefold from 12.6% in the 1980s to 36.8% in the 1990s.

A systematic review by Verbeteen and others sought to synthesize published literature on the potential association between childhood obesity and subsequent T1DM[183]. This review included peer reviewed articles whose exposure variable was obesity, BMI or another variable of weight-for height assessed after birth up to age 18 and the outcome was T1DM. Eight case control studies and one cohort study met their inclusion criteria. Four studies reporting results for childhood obesity as a categorical variable were pooled, meta-analysed and showed a positive association between childhood obesity and subsequent T1DM. Eight of the nine included studies individually reported a significant increase in risk or positive association between childhood obesity and T1DM in at least one group. The review was limited by wide variability in age groups at which the exposure variable was measured, and that all studies in the review were conducted in European[183]. The relevance of childhood obesity to T1DM risk in children of non-European origin is less clear.

Kaminski and associates compared the distribution of BMI among children developing T1DM to the general population and examined factors associated with BMI at the onset of T1DM[185]. Children between 2 and 18 years (N=490) enrolled in the Pediatric Diabetic Consortium were included in the study. Their BMI at diagnosis was compared with the general population and weight status was classified using the 2000 CDC population centiles as reference data[121,186]. Clinical and socio-demographic data were either retrieved from medical charts or obtained through interviews of the patients or their parents. To be included, participants had to have a clinical diagnosis of autoimmune T1DM with height and weight having been measured by a health care provider within fourteen days of diagnosis. Age at diagnosis, presence of diabetic ketoacidosis, weight, height, Tanner stage and HbA_{1C} measured within fourteen days of diagnosis were considered the clinical characteristics of interest at baseline. Analyses were performed with truncated data (±3 standard deviations) to verify that outliers did not have undue leverage.

Mean age at diagnosis was 9.5 years with an overall median BMI of 48^{th} percentile. Although overall, the T1DM patients had a slightly lower BMI compared to the general population, 11% were classified as overweight, 8% obese and 2% severely obese. Ethnicity (African America and Hispanic) as well as a lower HbA1c were associated with a higher BMI z-score at diagnosis while age, Tanner stage and DKA were not. Stratification by sex showed females but not males had significantly lower BMI than the 2000 CDC population.

2.15. Physical maturation and puberty for males and females

Results from previous studies indicate that puberty, a period characterised by physical maturation and the development of secondary sex characteristics [187,188] occurs at different ages for males and females[189,190]. It has also been previously reported that during puberty, females gain more fat cells than lean muscle mass while the opposite is true for males[123,191]. Furthermore, McCarthy et al reported that females gain more fat cells throughout life which predisposes them to pre-pubertal insulin resistance more than males[192]. Due to these differences, patterns of weight change for males and females may be different over time. These differences are important to consider when assessing any weight change that may be associated with initiation of insulin for T1DM patients.

Chapter 3: Study materials and methods

3.1 Description of Geographical area (Manitoba)

Manitoba is the most eastern of the Prairie Provinces. It borders the North West Territories and Nunavut to the north, Saskatchewan to the west, Ontario to the east and the United States of America to the south. In 2011, Manitoba's population was 1,208,268 representing 3.6% of the total Canadian population. The total number of children ages 0-18 was 386,400, representing 32.0% of Manitoba's population. Manitoba covers 552,329 square kilometres and is divided into five regional health authorities (RHAs) responsible for the delivery and administration of health services in specific geographical areas (Figure 1)[193]. Between 2002 and 2012, Manitoba had 11 RHAs, which were amalgamated into the five larger areas shown in Figure 5. A large proportion (54.9%) of people in Manitoba lives in Winnipeg, the provincial capital, where the Diabetes Education and Resource for Children and Adolescents (DER-CA) is located at the Health Sciences Centre Children's Hospital.

Figure 1: Map of Manitoba's five Regional Health Authorities

3.2 Description of data source

The Diabetes Education Resource for Children Adolescents (DER-CA) is located within the Children's Hospital of Winnipeg, at the Health Sciences Centre. The children's hospital is the only tertiary care pediatric referral centre for Manitobans, and also serves residents of northwestern Ontario and some from Saskatchewan[73]. Since 1986, the DER-CA program has maintained a comprehensive clinical database for all patients, representing a unique data resource because of the combination of the extensive clinical information on each patient (including measured height and weight) and the virtually universal coverage of the system. This study used the de-identified version of this database housed in the data repository at the Manitoba Centre for Health Policy (MCHP).

For all children and adolescents diagnosed with T1DM in Manitoba, diabetic treatment (insulin therapy) is initiated at DER-CA and on the few occasions that it is started elsewhere; clinicians at DER-CA are consulted on the initial regimen and dosage. DER-CA began to capture clinical data electronically on scheduled visits in 1993 and more consistently by 1997. Previous reports demonstrated that the DER-CA database ascertainment for incident cases of children with T1DM is 95-99 percent[69,194].

3.3 Data Collection methods

Measurement data was collected at every clinical visit by a trained nurse assistant. Patients are seen by clinicians on a quarterly basis (every 3 months) where individual heights and weights were measured using a calibrated Stadiometer. Patients were measured in bare feet, and in minimal clothing. In addition to these measurements, laboratory tests including HbA1c and insulin regimen are collected at every visit, although not consistently. One individual is responsible for entry of all chart data into the DER-CA electronic database.

3.4. Inclusion and exclusion criteria

The study population is comprised of children and youth in the DER-CA database diagnosed with T1DM between 1997 and 2012 by DER-CA pediatric endocrinologists; this included 1056 cases. The following exclusion criteria were then applied:

- Under age 2, or over age 18 years at diagnosis
- Followed at DER-CA for less than 6 months after diagnosis
- Did not reach at least age 16 before the end of the study period
- Those immigrating to Manitoba after initial diagnosis
- Those with biologically implausible BMI values (BMI z-score: <-4 or > 5) as defined by CDC growth charts at diagnosis[195,196].

A total of 440 patients met these criteria. An additional 61 patients were excluded because they did not have data recorded for a visit near the six month mark – which was used to define the initial weight change phase. These 61 patients did not differ significantly from the final sample of 379 in terms of age, sex, pubertal status or BMI Z-score at diagnosis.

3.5 Measurement of BMI

For children and adolescents, BMI measurement is adjusted for age and sex and compared to reference data using one of the three internationally recognized standard measures[119,150,151]. For this study, weight status was assessed using the sex and age adjusted BMI cut offs established by the CDC growth measures in 2000. The CDC growth charts are recommended by various professional organizations[197] as well as a previous study[148] for use in Canadian children and adolescents, and have been used by the DER-CA program for years. The key BMI measurements were those at diagnosis, at six months after diagnosis, and at graduation from the program (age 16 minimum).

3.6 Outcome variable

3.6.1 BMI z-score at graduation from DER-CA: Individual BMI values recorded at the last visit were converted into z-score, and analysed as a continuous variable.

3.7 Independent variable

Weight change in the six months after diagnosis was the independent variable, as measured by change in BMI Z-score. Because not all patients had a visit at exactly six months after diagnosis, a decision was made (in consultation with the pediatric endocrinologists at the DER-CA) to consider any visit between 4 and 8 months as the six-month visit. In the few cases where a participant had more than one visit within this period, the visit closest to 6 months was selected for use in the final analysis. Patients were classified into four groups according to their relative change in absolute weight (kgs) from baseline to six months after diagnosis:

- Stable: patients whose weight changed by less than 5% of their initial weight
- Weight loss: patients who lost 5% or more of their initial weight

- Moderate gain: patients who gained between 5% and 15% of their initial weight
- Large gain: patients who gained more than 15% of their initial weight

3.8 Control variables

3.8.1 Age at diagnosis: The child's age (in years) at diagnosis, entered as a continuous variable. Participants were also put in multi-year age groups (0-4; 5-9; 10-14 and 15 and over) to assess the potential mediating effects of age of diagnosis on BMI.

3.8.2 Duration of treatment: The length of time (in years) from diagnosis to the date of the patient's last visit. For this study, duration of treatment ranged from 2 to 15 years. Length of treatment was entered as a continuous variable. In consultation with DER-CA clinicians, the sample was also sub-divided into three categorical groups: 0-5 years, 6-9 years, or 10+ years.

3.8.3 Sex: Sex of each patient was obtained from DER-CA database records at diagnosis date and entered as a categorical variable.

3.8.4 BMI z-score at diagnosis: Every patient's baseline BMI was converted to a z-score at diagnosis, entered as a continuous variable. BMI values were derived from the DER-CA database and calculated from measured height and weight.

3.8.5 Puberty: For this study, puberty was defined as 10.5 years for females and 11.5 years for males, as done in previous studies[48,189]. Sub-group analyses were also performed separately for males and females, pre- and post-pubertal onset (at diagnosis).

3.8.6 DKA at diagnosis: This variable was created to identify patients who were in DKA at diagnosis. There were 85 (22.55%) individuals who presented with DKA at diagnosis. However, there was no difference in DKA vs. non-DKA patients in terms of the relationship between weight change in the first six months and final BMI, so this variable was not included in the final models.

3.8.7 Year of Referral: The study period was divided into two periods (1997-2000, and 2001-2012) to assess the potential effects of insulin analogues, which were introduced in 2001.

3.9 Data Analysis

Data were analysed on the secure server at MCHP using SAS 9.3. BMI z-scores and age at diagnosis were compared between groups using the independent sample student t-test for continuous variables. Analysis of variance using the GLM procedure was used to compare baseline BMI z-scores for multiple groups (the 4 weight change groups, and the 4 BMI groups). Chi-squared tests were used to compare categorical variables. Initial analyses were conducted in two time segments 1997-2000 and 2001-2012, to identify potential differences in clinical practice as a result of the introduction of insulin analogs in the year 2001. These analyses revealed no differences in the main patterns, so year of diagnosis was not included in the final model, and all patients were included.

While the pattern of change over time in the outcome variable (BMI) was expected to follow the same basic trajectory for most patients (increase), a degree of uncertainty remained until the actual data were accessed. To examine this possibility, initial exploratory work was done to

assess the data for potential heterogeneity. Important differences were found in 6-month weight change trends based on initial BMI and pubertal status. Therefore, the final analyses included these variables.

For the final analysis, the Generalized Linear Modeling (GLM) procedure was used to assess the association between change in BMI within 6 months after diagnosis, and BMI z-score at last visit. The models controlled for sex, duration of treatment, and BMI z-scores at diagnosis. Because the change in BMI values over time was shown to depend on pubertal status, separate models were also created based on this variable.

Two patients were excluded as outliers because they had extremely abnormal results which strongly affected the relationships between variables for the entire group. One patient had a very low initial BMI z-score (-2.42) and a very high final score (1.94), and another patient had a very high initial BMI z-score (2.57) and a very low final score (-1.41). It is possible that these values were the result of data collection or recording errors. Throughout this study, p-values less than 0.05 were considered statistically significant unless otherwise stated.

3.10 Ethics statement

This study was approved by the University of Manitoba Health Research Ethics Board (HREB #2013: 440), the Winnipeg Regional Health Authority's Research Review Committee, and the government of Manitoba's Health Information Privacy Committee (#2013/2014-49). The Manitoba Centre for Health Policy also approved the project through a signed researcher agreement (MCHP 2014-004). Standard protocols for using the DER-CA and MCHP databases

were followed throughout the duration of the project, as were proper procedures to ensure data were kept secure and confidential at all times. Study results are presented in summary form only, to ensure no individual data are identifiable.

Chapter 4: Results

4.1. Demographics

4.1.1. Patient characteristics

The results in Table 1 show the baseline characteristics of study participants at diagnosis, by BMI group.

Table 1: Baseline characteristics by BMI group

Characteristics	BMI groups at diagnosis					
	Total n= 377	**Underweight (n=33)**	**Normal weight (n=256)**	**Overweight (n=59)**	**Obese (n=29)**	**p-value**
Age at diagnosis (yrs)	11.99(0.16)	12.71(0.4)	12.04(0.21)	11.56(0.4)	11.61(0.57)	0.4
Length of treatment	5.42(0.16)	4.56(0.39)	5.39(0.21)	5.85(0.39)	5.77(0.56)	0.3
Age at last visit	17.33(0.02)	17.30(0.08)	17.35(0.03)	17.27(0.06)	17.28(0.08)	0.6
Sex N (%)						0.2
Female	161(42.7)	13(39.4)	117(45.7)	23(39)	8(27.6)	
Male	216 (57.3)	20(60.6)	139(54.3)	36(61)	21(72.4)	
Pubertal status N (%)						0.2
Pre-pubertal onset	128(33.95)	7(21.2)	84(32.8)	24(40.7)	13(44.8)	
Post-pubertal onset	249(66.05)	26(78.8)	172(67.2)	35(59.3)	16(55.2)	

Data in first three rows are means (SE); those in bottom four rows are number (%);

The rightmost column (p-value) shows the result of the statistical testing done to compare values for the four BMI groups. For the entire study group (n=377), the average age at diagnosis

was 11.99 ± 3.20 years (mean ± SD). Length of treatment ranged from 2-15 years with a mean of 5.42 ± 3.16 years (mean ± SD). At last visit, average age was 17.33 ± 0.47 years. Of the 377 patients, 216 (57.3%) were male, and 249 (66.1%) had post-pubertal onset of T1DM. There were no significant differences among any of the covariates for the four BMI groups at diagnosis. Pairwise comparisons for age at diagnosis, age at last visit and length of treatment did not reveal any significant differences. Length of treatment was slightly shorter for patients in the underweight BMI group compared to those in the overweight group, though this difference did not quite reach statistical significance (p=0.06).

Males appeared to be more overweight and obese at diagnosis, though this difference was also not significant (p=0.2). At diagnosis, 72.4% of those in the obese group, and 61% of those in the overweight group were males. Patients with post- pubertal onset tended to be thinner than their pre-pubertal counterparts, with more than three times as many patients in the underweight category, (78.8%), but this difference also did not reach statistical significance (p=0.2). A higher proportion of patients with post-pubertal onset were normal weight (67.2%), overweight (59.3%), or obese (55.2%) than those with pre-pubertal onset of T1DM.

4.1.2 Comparison between male and female patients

Table 2 shows a comparison of covariates between male and female patients.

Table 2: Comparison of covariates between sexes

Characteristics	Female (n=161)	Male (n=216)	p-value
Age at diagnosis (yrs)	11.89(0.24)	12.06(0.23)	0.6
BMI z-score at diagnosis	0.23(0.08)	0.31(0.07)	0.4
BMI z-score six months after diagnosis	0.56(0.06)	0.50(0.06)	0.4
BMI z-score at last visit	0.82 (0.05)	0.54(0.06)	0.0008**
Length of treatment at last visit	5.51(0.24)	5.35(0.22)	0.6
Age at last visit	17.31(0.04)	17.34(0.03)	0.6
Pubertal status N (%)			0.1
Pre-pubertal onset	48(29.8)	80(37)	
Post-pubertal onset	113(70.2)	136(63)	
Weight change groups N (%)			0.2
Weight loss	7(4.4)	6(2.8)	
Stable	24(14.9)	40(18.5)	
Moderate gain	67(41.6)	106(49.1)	
Large gain	63(39.1)	64(29.6)	

Age, and BMI z-score at diagnosis, and BMI z-score six months after diagnosis did not differ by sex. At last visit however, females had significantly higher BMI z-score (p=0.0008) compared to males. Length of treatment and age at last visit were not significantly different. A higher proportion (70.2%) of females and males (63%) had post-pubertal onset of T1DM, but the difference did not reach statistical significance (p=0.1). A higher proportion of males had either stable weight (18.5%) or moderate gain (49.1%) by six months after diagnosis. The proportion of female and male patients in the weight loss or large gain groups was almost identical. There were no statistically significant sex differences by weight change group (p=0.2)

4.1.3 Comparison of patients diagnosed before versus after puberty

Results comparing covariates by pubertal status are presented in Table 3.

Table 3: Comparison of patients diagnosed before versus after puberty

Characteristics	Pre-pubertal onset (n=128)	Post-pubertal onset (n=249)	p-value
BMI z-score at diagnosis	0.49(0.09)	0.17(0.07)	0.0036**
BMI z-score six months after diagnosis	0.56(0.08)	0.51(0.05)	0.6
BMI z-score at last visit	0.76(0.07)	0.61(0.05)	0.1
Length of treatment at last visit	9.08(0.18)	3.53(0.1)	<.0001***
Age at last visit	17.30(0.04)	17.34(0.03)	0.3
Sex N (%)			0.2
Female	48(37.5)	113(45.4)	
Male	80(62.5)	136(54.6)	
Weight change groups N (%)			0.02*
Weight loss	s (2.4)	s (4)	
Stable	15(11.7)	49(19.7)	
Moderate gain	73(57)	100(40.2)	
Large gain	37(28.9)	90(36.1)	

Data in first five rows are means (SE) those in the last six rows are number (%)
's': indicates value suppressed to ensure confidentiality

Results in Table 3 show that patients with pre-pubertal onset of T1DM had significantly higher BMI z-scores at diagnosis compared to those with post-pubertal onset (p=0.0036). Six months after diagnosis, BMI z-scores were no longer significantly different by pubertal status (p=0.6). At the last visit, patients with pre-pubertal onset tended to have higher BMI z-score than their post-pubertal counterparts but the difference was not statistically significant (p=0.1). However, there were differences when the samples were also split by sex: pre-pubertal females had significantly higher BMI z-scores (p=0.04) than post-pubertal counterparts (not shown in Table 3).

There were no significant BMI z-score differences for males by pubertal status at diagnosis (p=0.4). As expected, follow-up was significantly longer (p <0001) for patients with pre-pubertal onset compared to those with post- pubertal onset. On average, patients who were pre-

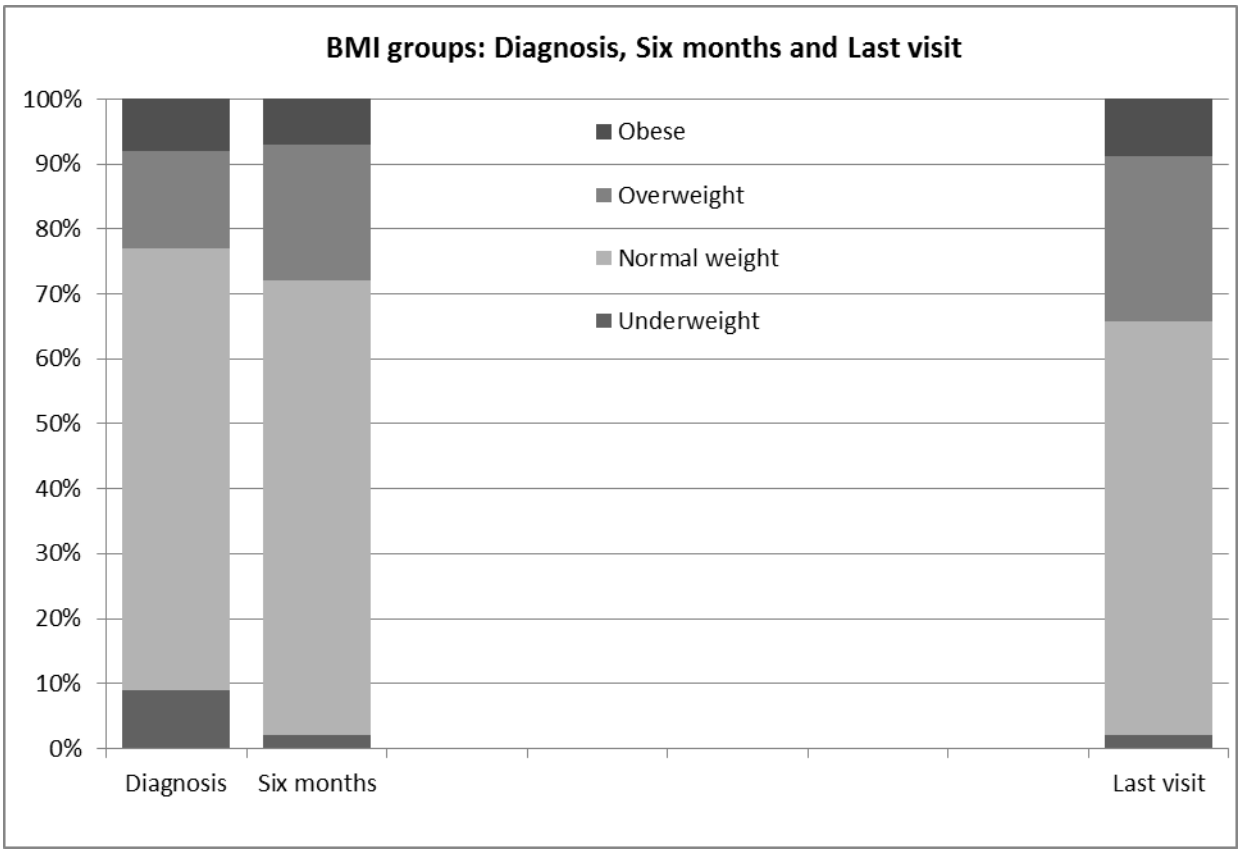
pubertal at diagnosis were followed up for 5.6 years longer than those who were post-pubertal. Age at last visit did not significantly differ by pubertal status (p=0.3). There were more males than females in both groups, though the difference was higher for those diagnosed before puberty (62.5% male) than those diagnosed after (54.6%). These proportions were not statistically different from each other (p=0.2). There were significantly more patients diagnosed after puberty in all but the moderate gain group (p=0.02).

4.2 Prevalence of underweight, overweight and obesity

4.2.1 BMI groups for all patients

Figure 2 shows the proportion of patients in each BMI group at diagnosis, six months later and at last visit.

Figure 2: BMI groups for all patients



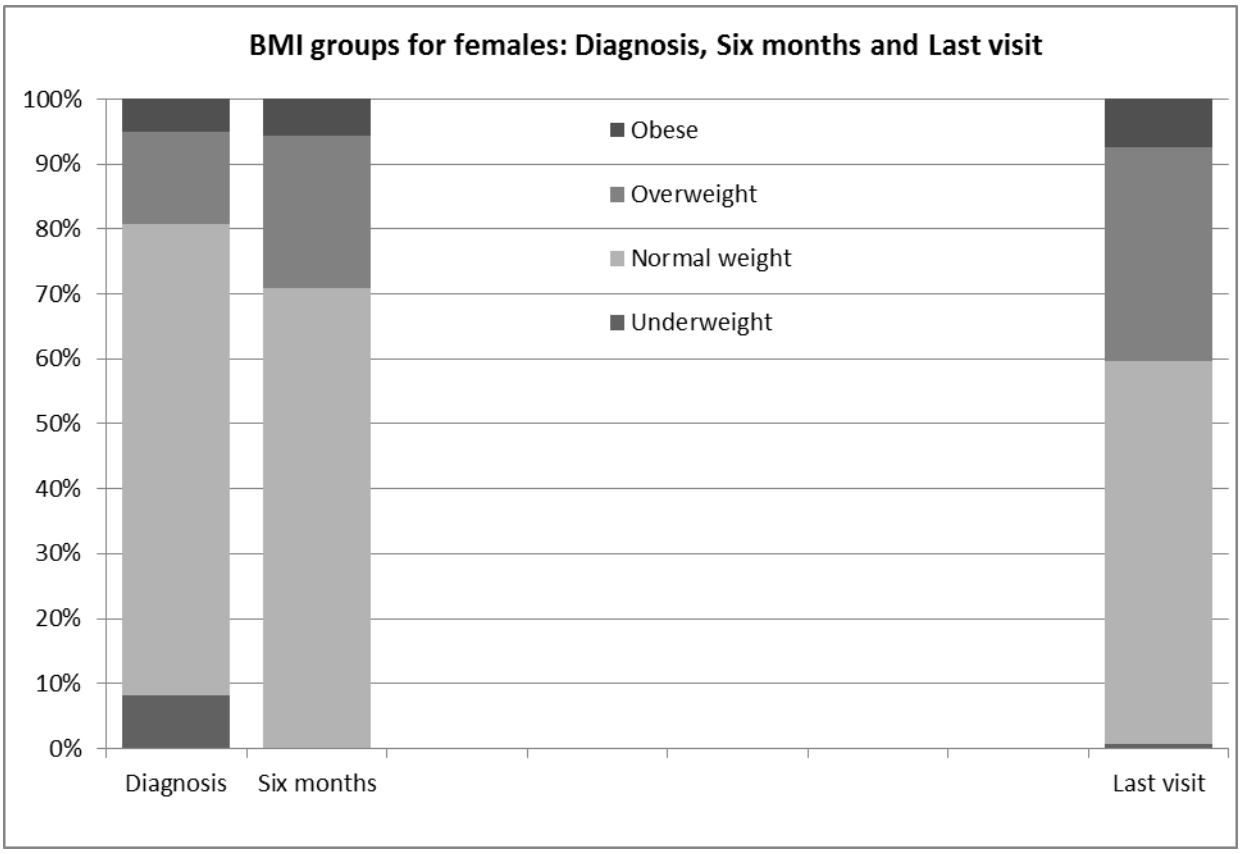
At diagnosis, 9% were underweight, 68% were normal weight, 15% were overweight and 8% were obese. Six months after diagnosis, only 2% of the patients were underweight, 70% were in the normal weight group, 21% overweight and 7% were obese. As the proportion of underweight patients became smaller six months after diagnosis, the overweight BMI group increased by 6%, while the normal weight and obese groups remained relatively unchanged. This suggests that as weight change occurred, some patients moved from one BMI group to the other. At the last visit, the underweight group remained at 2%, normal weight dropped to 65%, overweight increased to 26% and the obese group increased to 9%. The proportion of overweight steadily increased overtime, while underweight decreased after six months and

then stabilized thereafter. The proportion in the normal weight group went down, while the proportion in the obese group remained relatively unchanged over time.

4.2.2 BMI groups for female patients

The proportion of females in each BMI group over time is presented in Figure 3.

Figure 3: BMI groups for females



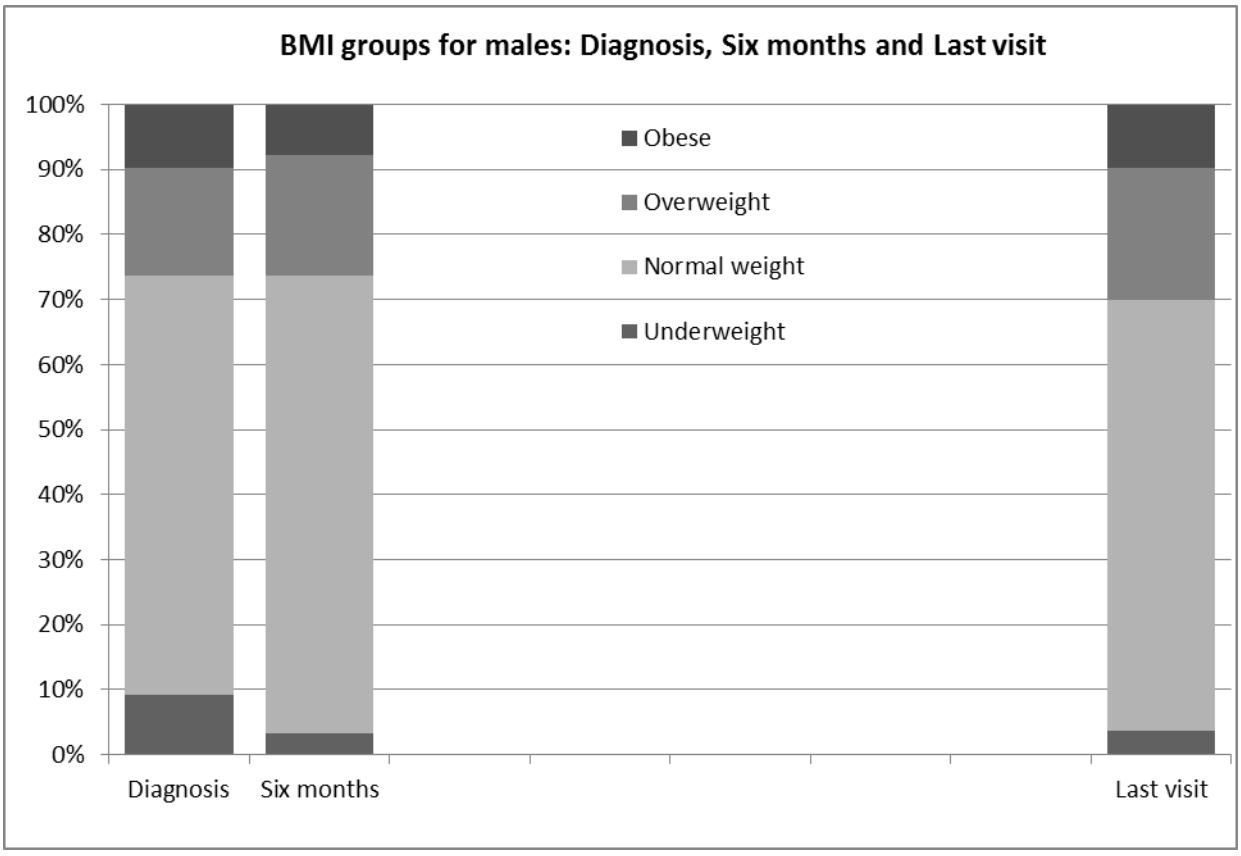
At diagnosis, 8% of females were underweight, 73% normal weight, 14% overweight and 5% were obese. Six months later, none of the females were underweight, 71% were in the normal weight group, 23% were overweight and 6% were obese. At their last visit, 60% of the females were in the normal weight group, 33% overweight and 7% were obese. As the overweight and obese groups increased, the normal weight group became smaller over time, and the

underweight group disappeared. From diagnosis to last visit, the proportion of overweight females increased by 19%, and the normal weight group decreased by 13%.

4.2.3 BMI groups for male patients

Figure 4 shows the proportion of males in each BMI group at diagnosis, six months later and at the last visit.

Figure 4: BMI groups for males



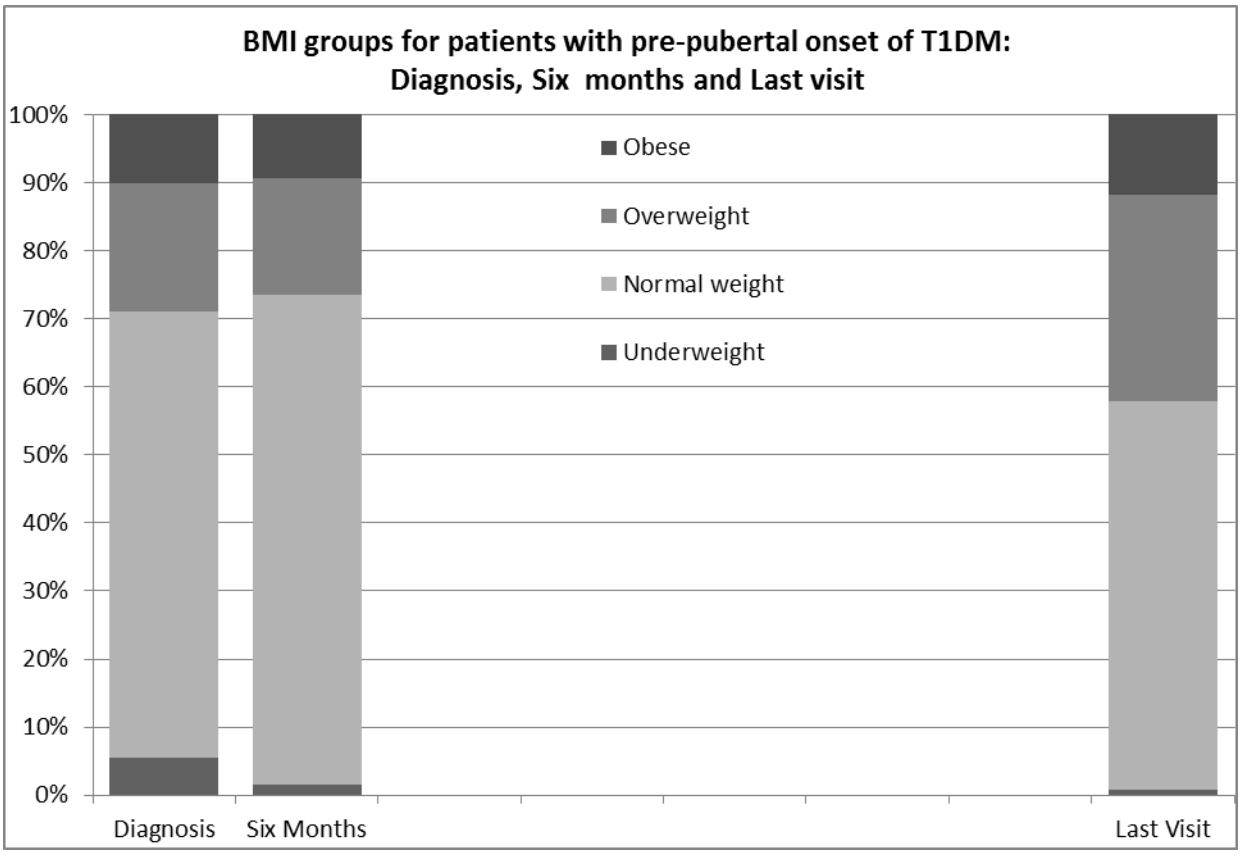
At diagnosis, 9% of males were in the underweight group, 64% had normal weight, 17% were overweight and 10% were obese. Six months after diagnosis, only 3% of male patients were underweight, 70% were in the normal weight group, 19% were overweight and 8% were obese. At their last visit, 4% of males were underweight, 66% had normal weight, 20% were overweight and 10% were obese. Overall, BMI group membership among males did not change

much over time. From diagnosis to the last visit, overweight increased, but only by 3%; the obese and normal weight groups were stable, and the underweight group decreased.

4.2.4 BMI groups for patients with pre-pubertal onset of T1DM

Figure 5 shows the distribution of patients with pre-pubertal onset of T1DM across the four BMI groups over time.

Figure 5: BMI groups for patients with pre-pubertal onset of T1DM



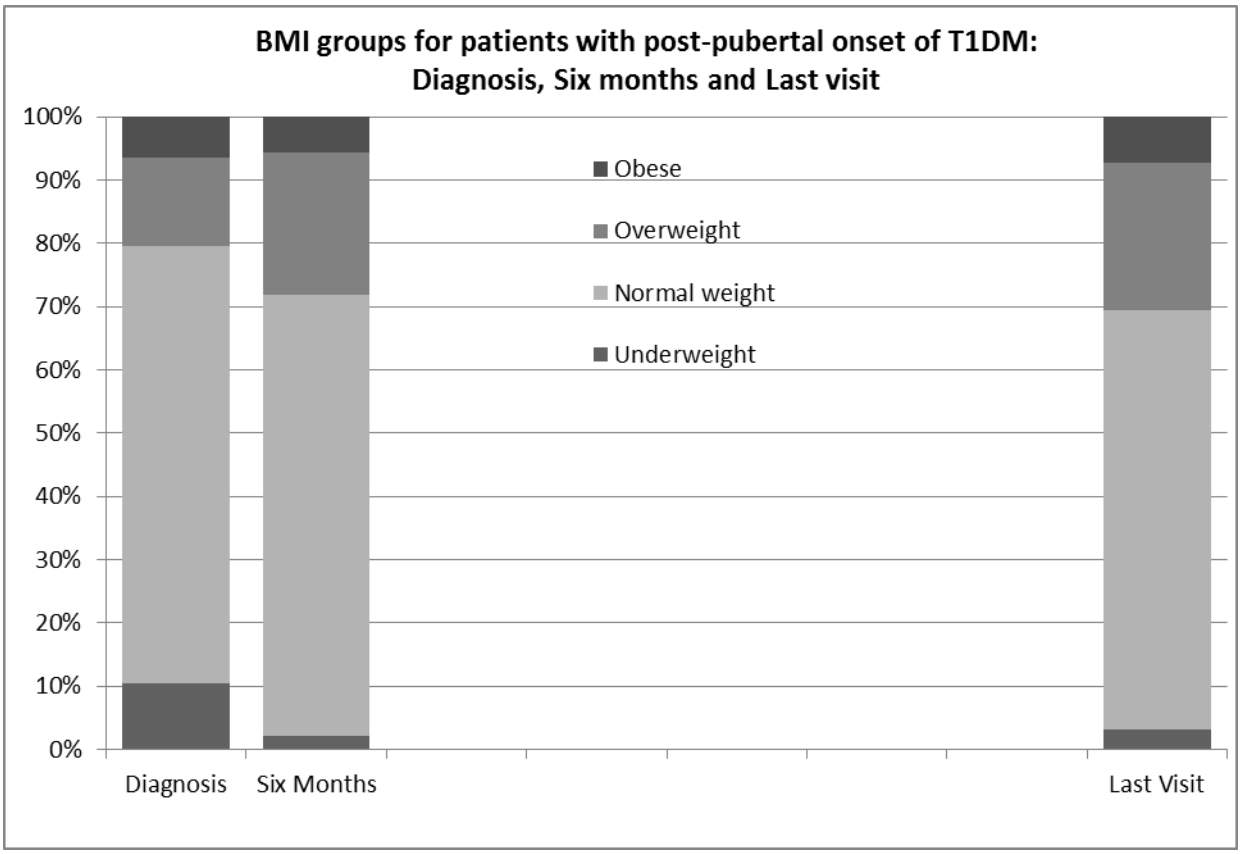
At diagnosis, 5% of the patients with pre-pubertal onset were underweight, 66% had normal weight, 19% were overweight and 10% were obese. Six months after diagnosis, 1.5% were underweight, 71.9% had normal weight, 17.2% were overweight, and 9.4% were obese. At last visit, 57% of those with pre-pubertal onset were normal weight, 30% were overweight and 12% were obese. Only 1% of those with pre-pubertal onset were underweight at last visit. Obesity

remained relatively stable over time, increasing only by 2% from 10% at diagnosis to 12% at the last visit. Underweight steadily decreased from 5% at diagnosis to just below 1% at the last visit.

4.2.5 BMI groups for patients diagnosed after post-pubertal onset

Figure 6 represents the distribution of patients diagnosed after post-pubertal onset across the four BMI groups.

Figure 6: BMI groups for patients with post-pubertal onset of T1DM



At diagnosis, 10.4% of the patients were underweight, 69.1% normal weight, 14.1% overweight and 6.4% were obese. Six months after diagnosis, only 2% were underweight, 70% were normal weight, 22% were overweight and 6% were obese. Overweight increased by 8% as underweight dropped by a similar percentage. At the last visit, 3.2% of patients were underweight, 66.3%

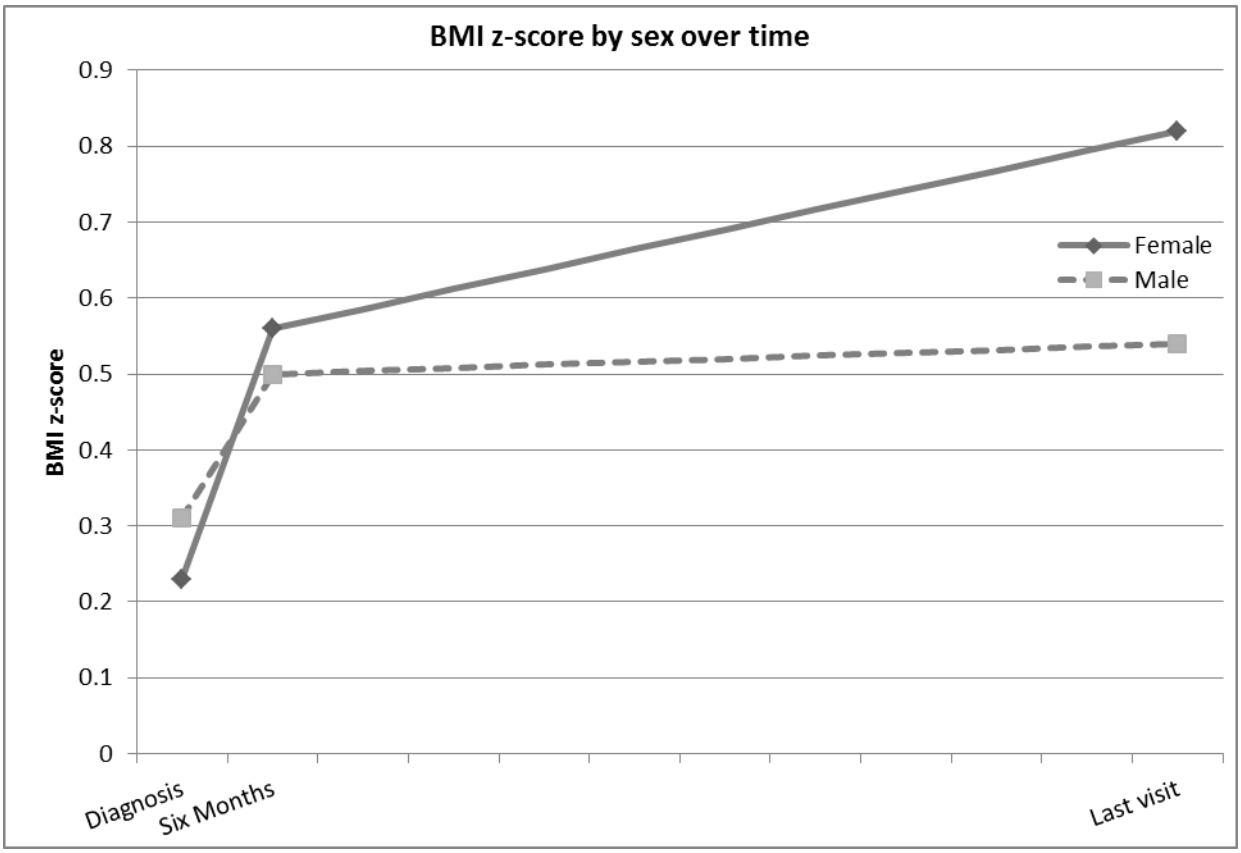
had normal weight, 23.3% were overweight and 7.2% were obese. Over time, only the overweight group had a large (9%) increase; the other three groups had small changes.

4.3 Change in BMI z-score over time

4.3.1 Change in BMI z-score over time, by sex

The change in BMI z-score over time varied according to sex, pubertal status and BMI z-score at diagnosis. Figure 7 shows the changes in average BMI z-score from diagnosis to the last visit, by sex.

Figure 7: Change in BMI z-score over time by sex



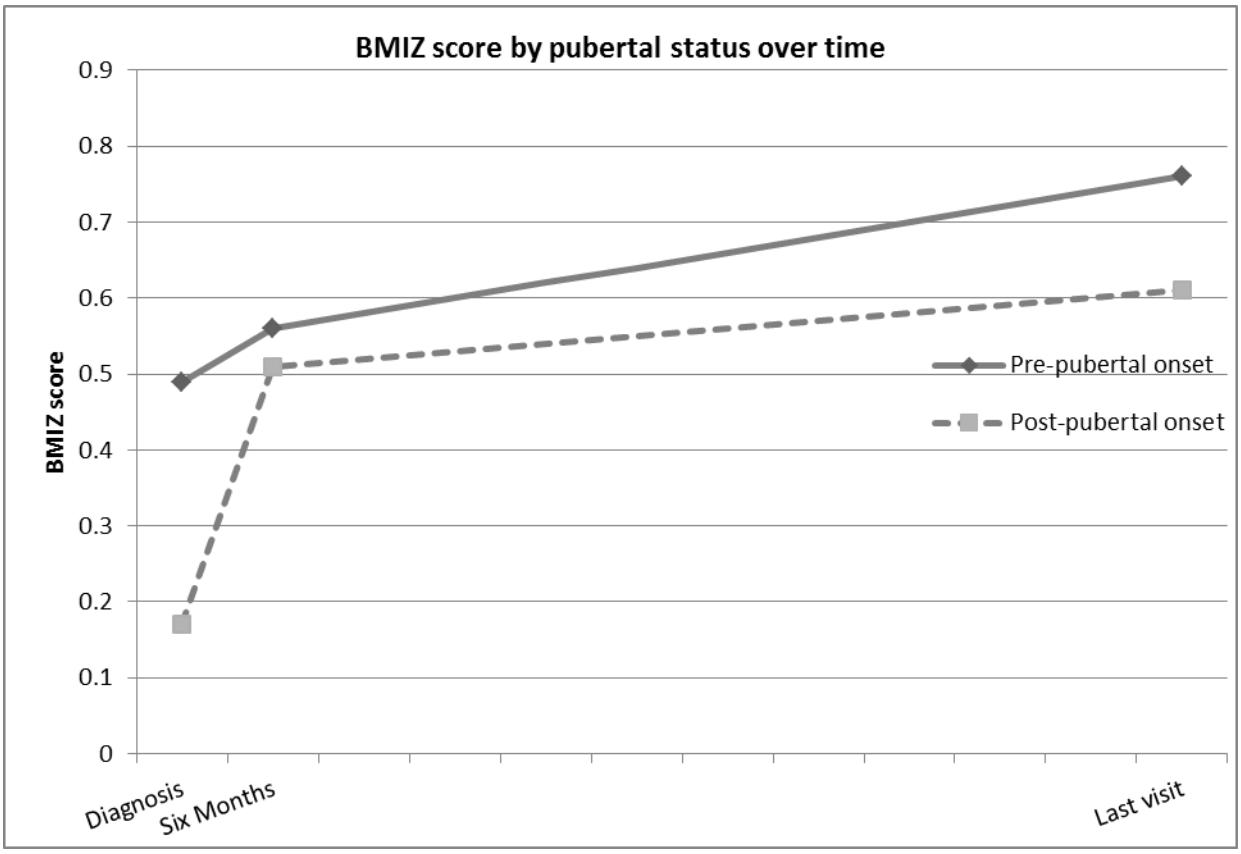
Males had a higher BMI z-score than females at diagnosis. Over time however, females gained weight more rapidly and their average BMI z-score rose above the male z-score around six months after diagnosis. Whereas the BMI z-score for males plateaued six months after

diagnosis, the female BMI z-score continued to increase to the last visit. At last visit, the average BMI z-score for females was higher (0.82) than their male counterparts (0.54).

4.3.2 Change in BMI z-score over time by pubertal status

The change in average BMI z-score over time by pubertal status is presented in Figure 8.

Figure 8: Change in BMI z-score over time by pubertal status



Patients with pre-pubertal onset had higher BMI z-score at diagnosis and remained above their post-pubertal counterparts throughout the duration of follow up. Their BMI z-scores steadily increased over time. For those with post-pubertal onset of T1DM, average BMI z-score rose quickly from diagnosis to six months, and then levelled off approaching the time of the last visit. At last visit, the average BMI z-score for patients with pre-pubertal onset of T1DM was 0.76

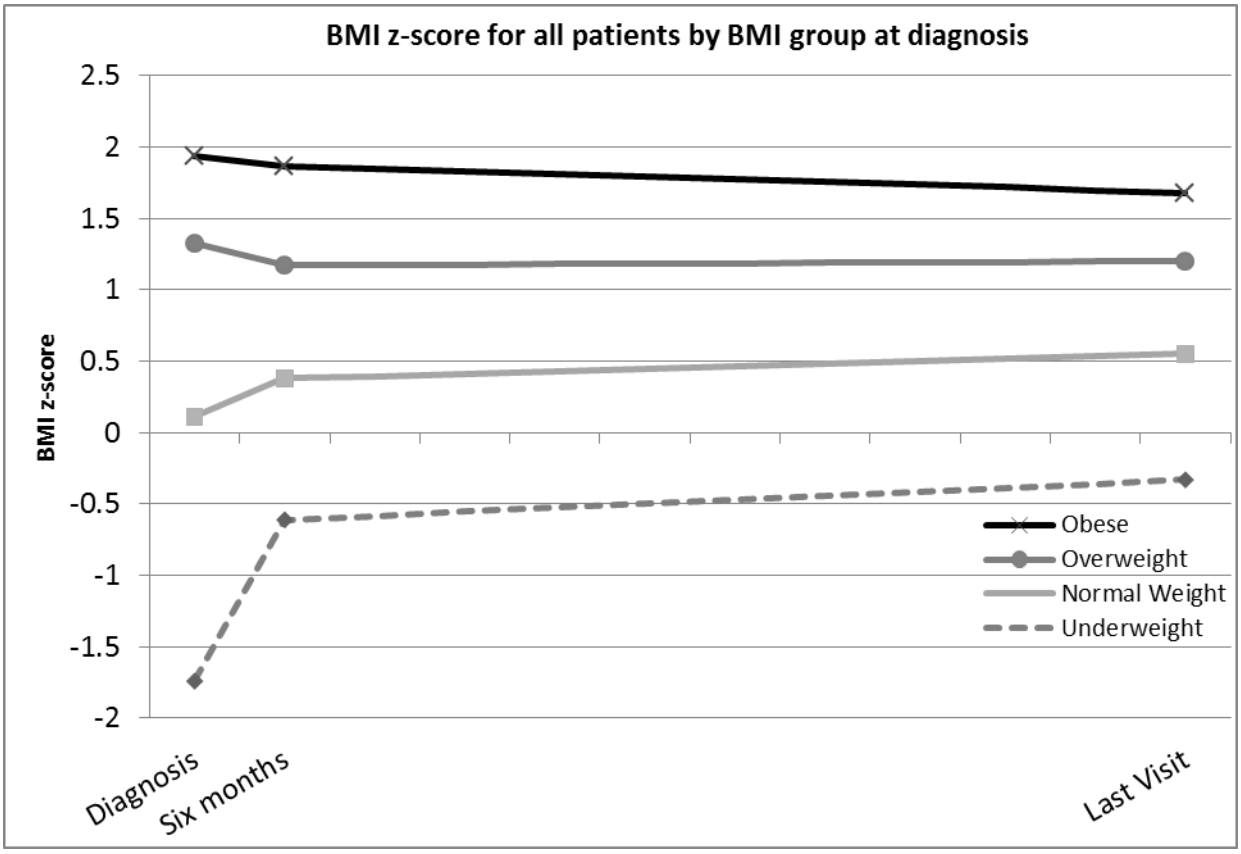
compared to 0.61 for those with post-pubertal onset, but the difference was not statistically significant.

4.4. Change in BMI z-score over time by BMI group at diagnosis

4.4.1 Change in BMI z-score for all patients by BMI group at diagnosis

Figure 9 shows changes in average BMI z-score for all patients by their BMI group at diagnosis.

Figure 9: Change in BMI z-score for all patients by BMI group at diagnosis

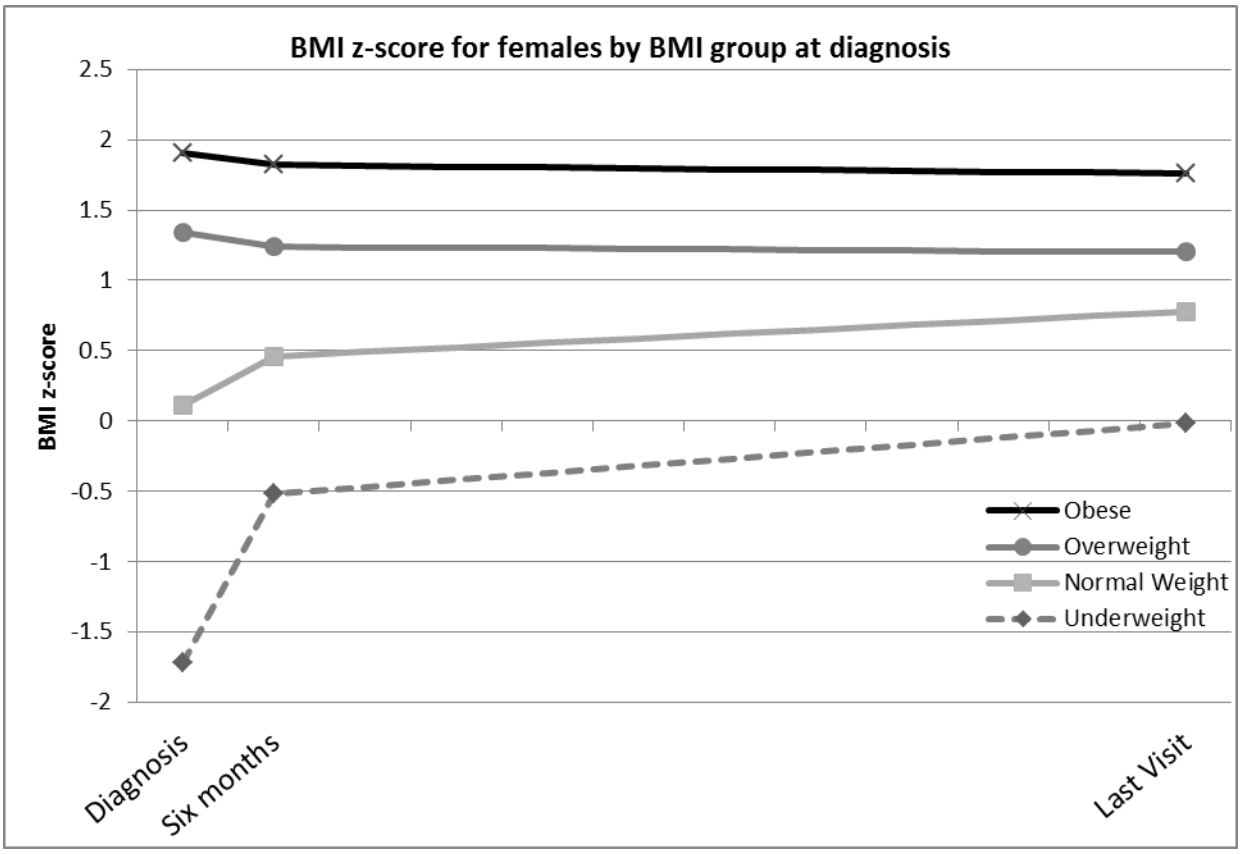


Overall, individuals who were underweight at diagnosis gained the most weight, followed by those in the normal weight group. The pattern of BMI z-score change for patients who were obese and overweight at diagnosis shows a decline in the six months following diagnosis, and the obese group continued to lose weight up to their last visit.

4.4.2 Change in BMI z-score for females by BMI group at diagnosis

The change in BMI z-scores by BMI group at diagnosis for females over time is shown in Figure 10.

Figure 10: Change in BMI z-score for females by BMI group at diagnosis

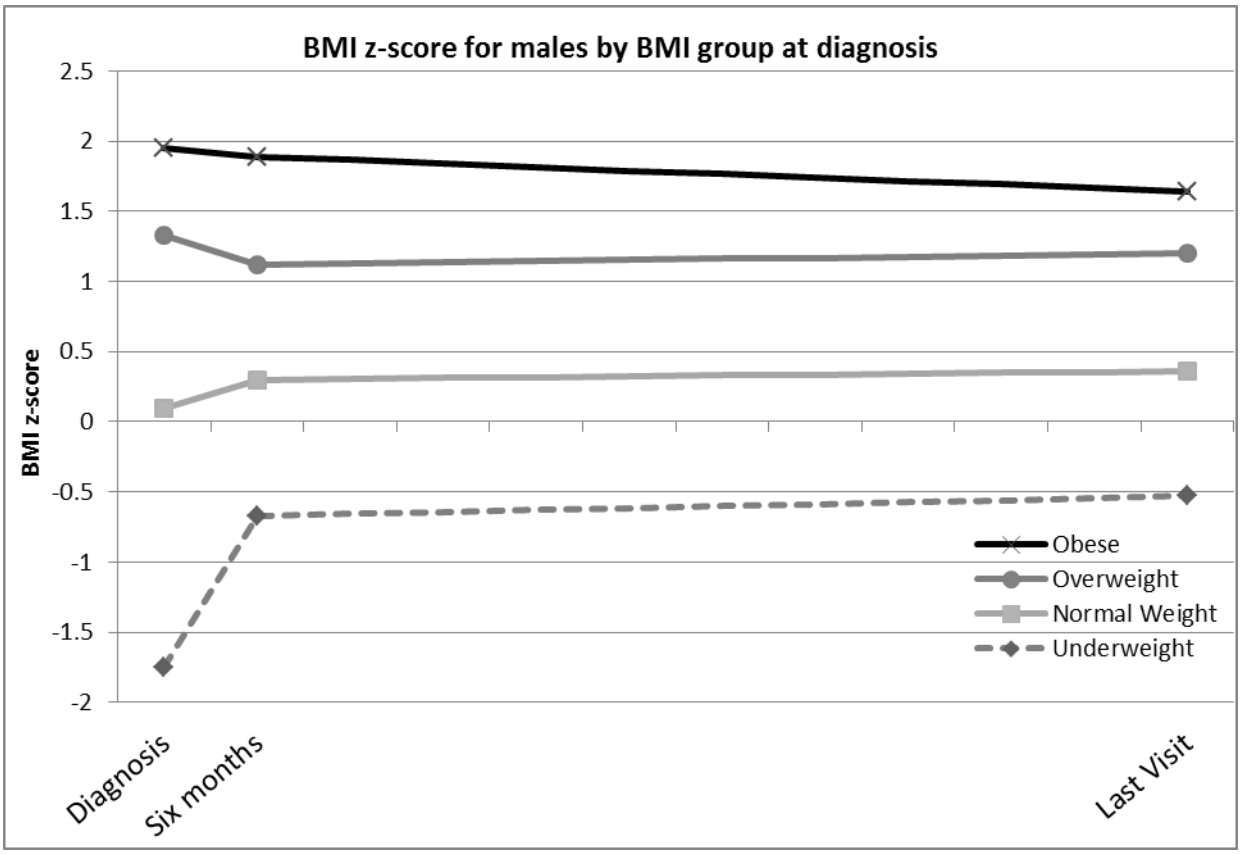


Females who were underweight at diagnosis gained the most weight followed by those in the normal weight group. Both groups appear to be still gaining weight at the time of the last visit. The BMI z-score for female patients who were overweight and obese at diagnosis did not change much. The trend of their BMI z-score change shows a small downward trajectory overtime.

4.4.3 Change in BMI z-score over time for males by BMI group at diagnosis

Figure 11 shows the change in BMI z-score for male patients by BMI group at diagnosis, over time.

Figure 11: Change in BMI z-score for males by BMI group at diagnosis

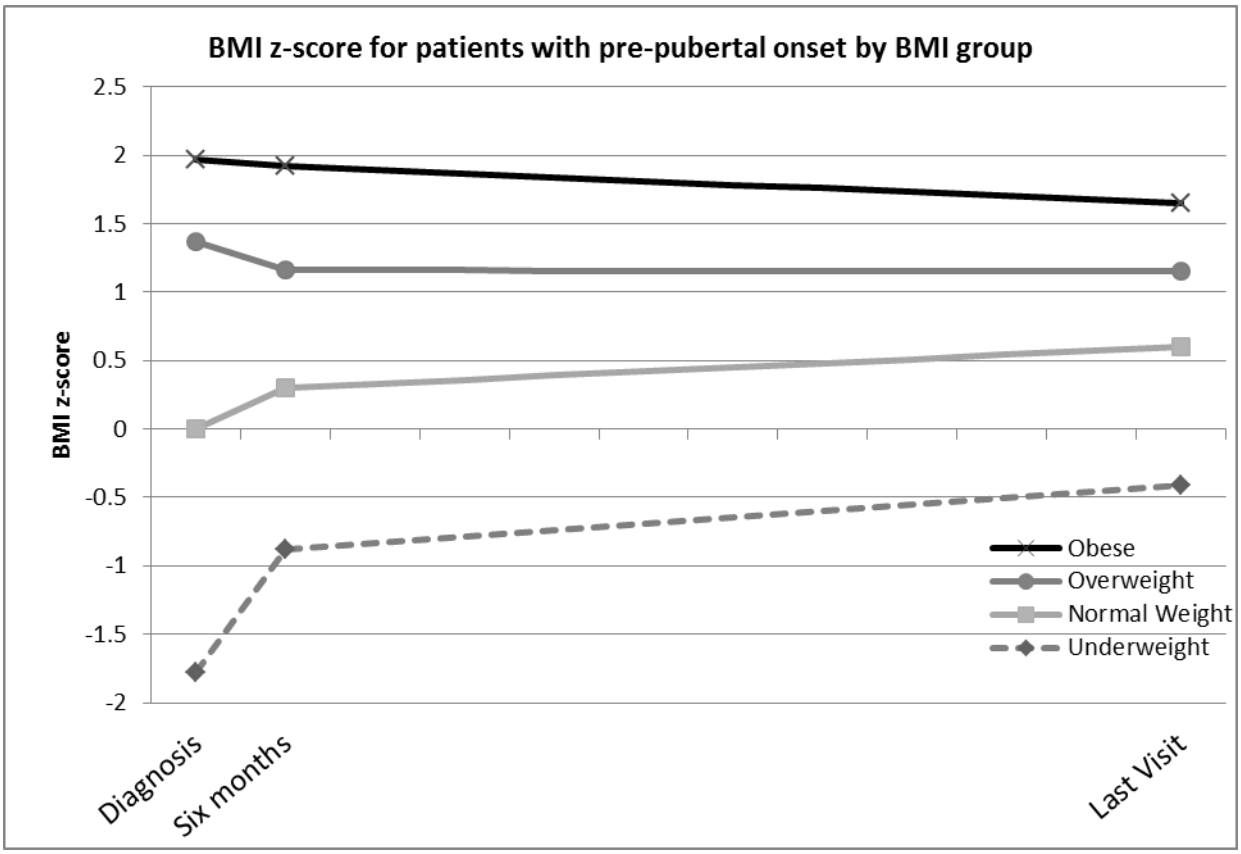


As was seen with females, males in the underweight group gained the most weight over time, followed by the normal group – though in both cases, the BMI z-score changes were smaller than for females, indicating less weight gain. Moreover, both groups appear to have reached stable BMI z-scores by the time of the last visit. BMI z-scores for overweight males decreased in the six months after diagnosis but began to increase slightly towards their last visit. BMI z-scores for obese males appeared not to change much in the six months following diagnosis, but decreased thereafter.

4.4.4 Change in BMI z-score for patients with pre-pubertal onset of T1DM

Figure 12 shows the trajectory of BMI z-score changes over time by BMI group, for patients diagnosed before puberty.

Figure 12: Change in BMI z-score for patients with pre-pubertal onset by BMI group

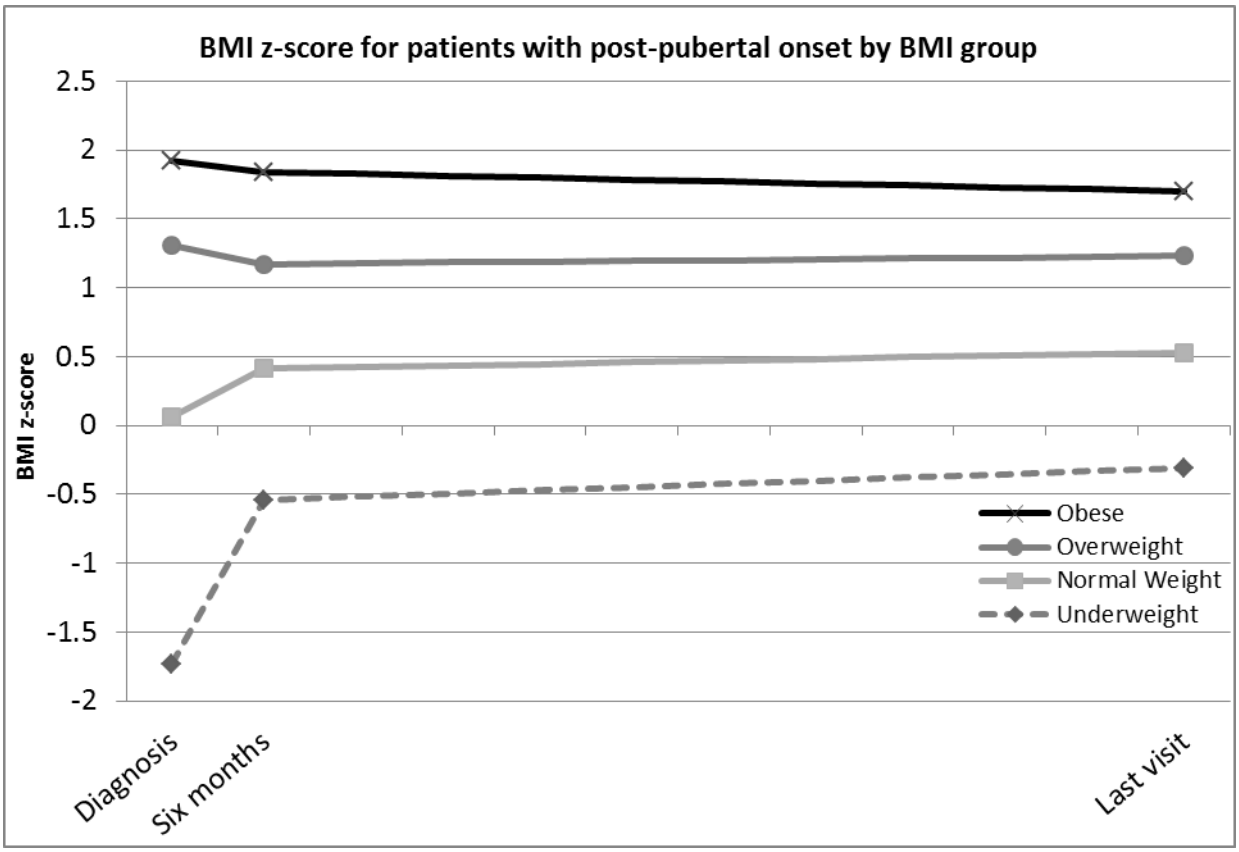


Average BMI z-score for the underweight and normal weight groups show steady and continued increase over time from diagnosis to the last visit. Average BMI z-score changes for the overweight and obese groups appear to resemble that of the males.

4.4.5 Change in BMI z-score for patients with post-pubertal onset by BMI groups at diagnosis

Changes in average BMI z-scores over time for patients with post-pubertal onset of T1DM are presented by BMI group in Figure 13.

Figure 13: Change in BMI z-score for patients with post-pubertal onset of T1DM by BMI group



These results seem to suggest that for patients diagnosed after puberty, there were higher proportions of males in underweight and normal weight groups, and females in the overweight and obese groups.

4.5 Change in BMI z-score by weight change groups

4.5.1 Comparison of covariates by weight change groups

Changes in BMI z-score were also assessed using groups based on the magnitude of each patient's relative weight change during the six months after diagnosis. Table 4 shows a comparison of covariates for the four weight change groups.

Table 4: Comparison of covariates by weight change groups

		Weight change groups				
	Total n=377	**Weight loss (n=13)**	**Stable (n=64)**	**Moderate gain (n=173)**	**Large gain (n=127)**	**p-value**
Age (years)	11.99(0.16)	13.23(0.84)	13.01(0.4)	11.44 (0.26)	12.10(0.25)	0.0031**
BMI z-score at diagnosis	0.28(0.05)	1.35(0.17)	0.73(0.1)	0.40(0.07)	-0.23(0.09)	< 0.0001**
Length of treatment at last visit (yrs)	5.42(0.16)	4.31(0.77)	4.43(0.1)	5.98(0.25)	5.26(0.25)	0.0030**
Age at last visit (yrs)	17.33(0.03)	17.31(0.28)	17.30(0.06)	17.35(0.04)	17.31(0.04)	0.7
BMI z-score six months after diagnosis	0.53(0.04)	0.51(0.24)	0.44(0.1)	0.47(0.07)	0.65(0.07)	0.2
BMI z-score at last visit	0.66(0.04)	0.75(0.28)	0.64(0.1)	0.61(0.07)	0.73(0.07)	0.6
Sex N (%)						
Female	161(42.7)	7(53.8)	24(37.5)	67(38.7)	63(49.6)	0.2
Male	216(57.3)	6(46.2)	40(62.5)	106(61.3)	64(50.4)	
Pubertal status N (%)						
Pre-pubertal onset	128(34)	s (23.1)	s(23.4)	73(42.2)	38(29.1)	0.02*
Post-pubertal onset	249(66)	10(76.9)	49(76.6)	100(57.8)	90(70.9)	

Data in first six rows are means (SE); those in the last four rows are number (%)
Stable: patients whose weight changed by less than 5% of their initial weight
Weight loss: patients who lost 5% or more of their initial weight
Moderate gain: patients who gained between 5% and 15% of their initial weight
Large gain: patients who gained more than 15% of their initial weight
's': indicates value suppressed to ensure confidentiality

Only 13 patients lost more than 5% of their original weight (kgs), 17% had stable weight, 47% had moderate gain and 32% had large weight gain. At diagnosis the four groups were significantly different on age (p=0.003), BMI z-score (P<.0001) and length of treatment (p=0.003). Patients with moderate weight gain were youngest followed by those with large gain

while those who lost weight were oldest at diagnosis. Pairwise comparisons revealed that moderate weight gainers were significantly younger than those in the stable (p=0.0008) and weight loss (p=0.05) groups.

Average BMI z-scores were lowest for patients who had large weight gain and highest for those who lost weight in the six months following diagnosis. Average length of treatment was shortest for patients in the weight loss group, and longest for the moderate weight gainers. Pairwise comparisons revealed that patients in the moderate gain group had significantly longer follow up than those with stable weight (p=0.0007), and those in the large gain group (p=0.05). The moderate gain group also had longer follow up duration than those in the weight loss group but the difference did not reach statistical significance (p=0.06).

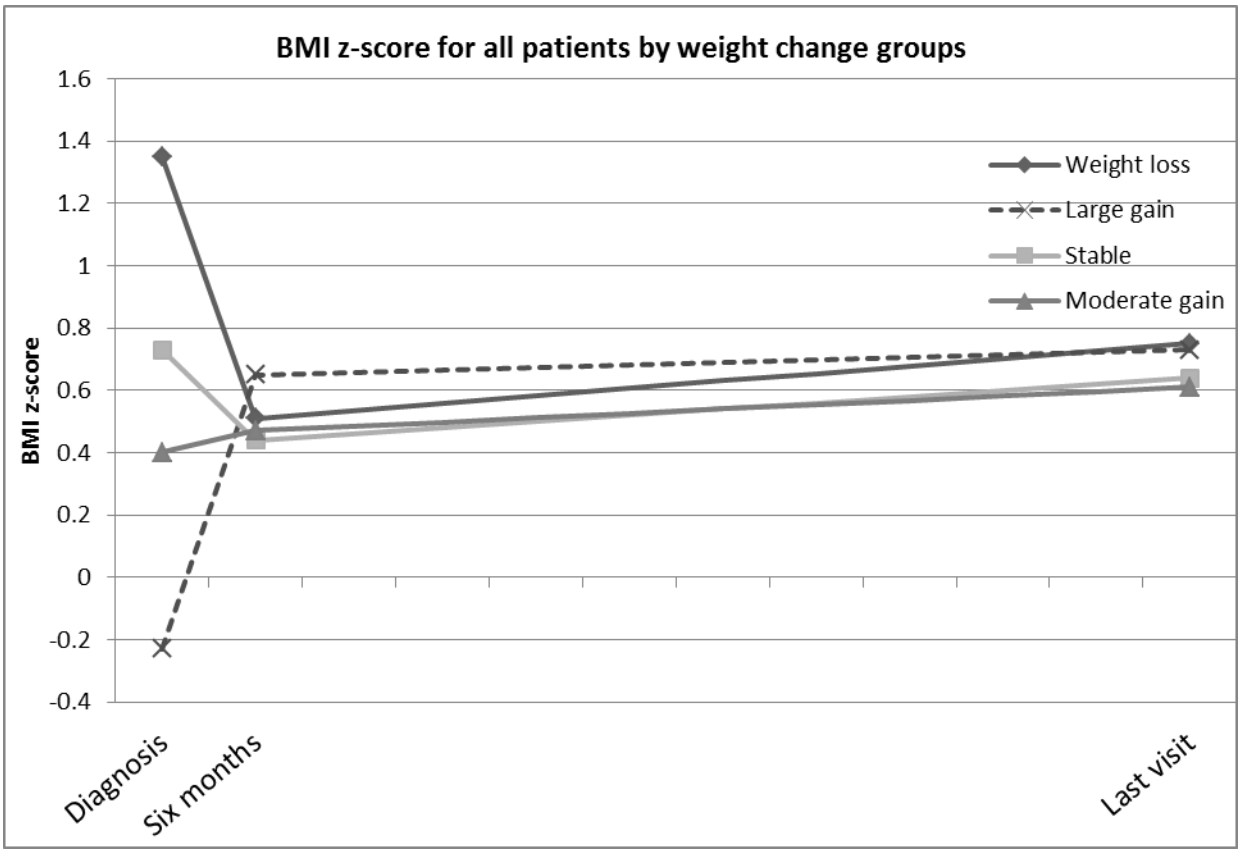
At the last visit, there were no significant age (p=0.7) or BMI z-score (p=0.6) differences among the four groups. Six months after diagnosis, average BMI z-scores for patients who had large weight gain tended to be higher (p=0.2) although it did not reach statistical significance. Pairwise comparisons showed that six months after diagnosis, large weight gainers had higher (but not statistically significant) BMI z-scores than those in the stable weight group (p=0.09) and moderate gainers (p=0.07). There were higher proportions of males than females with moderate weight gain (61.3%) and stable weight (62.5%), although the difference did not reach statistical significance (p=0.2). There was a significantly higher proportion of patients with post-pubertal onset of T1DM in each of the four weight change groups (p=0.02). Most (91.3%) but not all patients gained weight in the six months after initiation of insulin therapy. None of the

8.7% who lost weight during this period had been underweight at diagnosis (not shown in Table 4).

4.5.2 Change in BMI z-scores by weight change groups

Figure 14 shows trends in BMI z-scores over time by weight change group.

Figure 14: Change in BMI z-score for all patients by weight change group



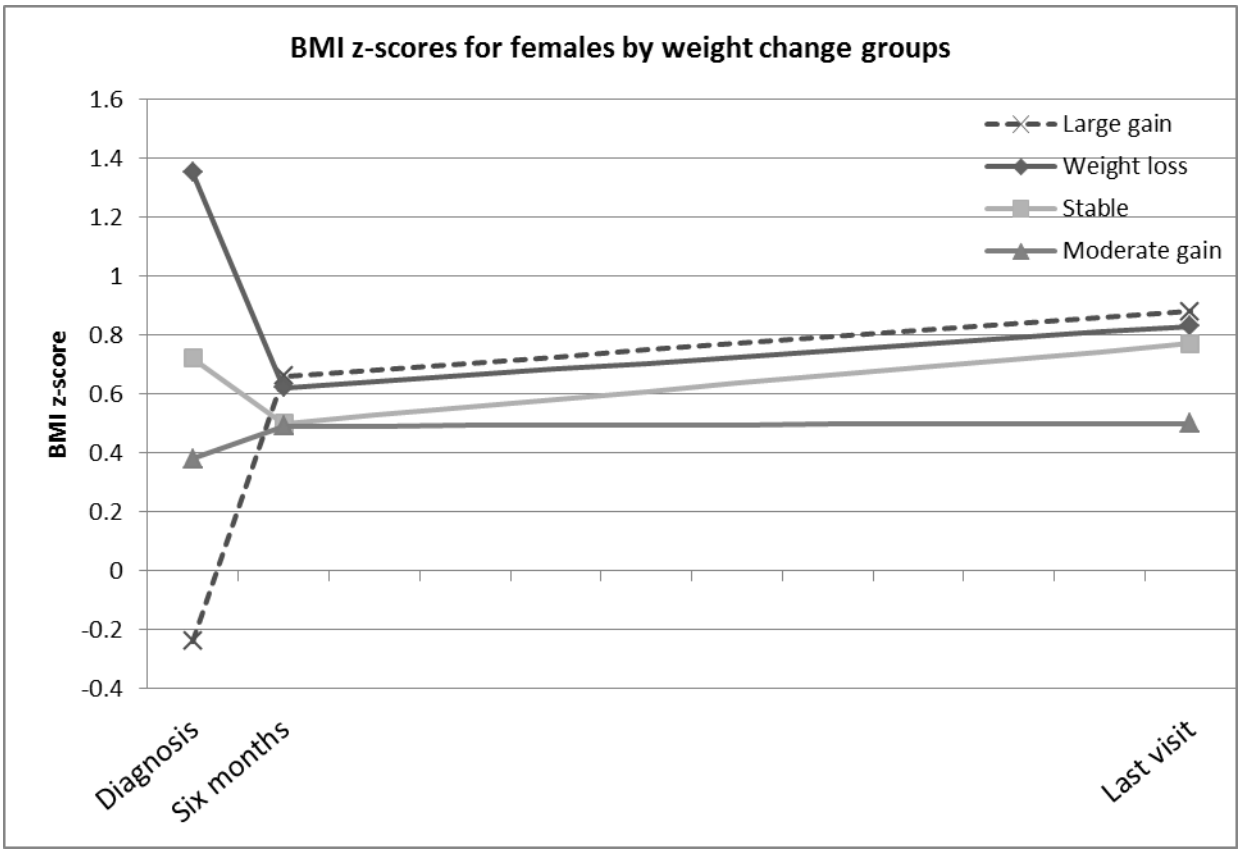
By six months after diagnosis, BMI z-score for all but the large gain group tended to converge around 0.5 and levelled off, with very little variability at last visit. At six months, the average BMI z-score for patients in the large gain group was highest (0.65). The weight loss group regained some weight after their dramatic reduction in the first six months on insulin, and ended with higher BMI z-scores than the other groups. The stable group lost weight in the first six months following diagnosis and regained some of it thereafter, but not as much as the

weight loss group. The moderate gain group had a distinctly more linear and steady weight gain over time and ended with the lowest average BMI z-scores of the four groups. Average BMI z-scores for the large gainers surpassed all other groups by six months after diagnosis. They gained only a small amount thereafter before reaching plateau by their last visit. The stable weight and moderate weight gain groups had the least variability in BMI z-score changes over time, and both groups ended with slightly lower average BMI z-score than the other two groups at the last visit.

4.5.3 Change in BMI z-score for females by weight change groups

Average BMI z-score changes for females by the relative weight change groups are presented in Figure 15.

Figure 15: Change in BMI z-score for females score by weight change group

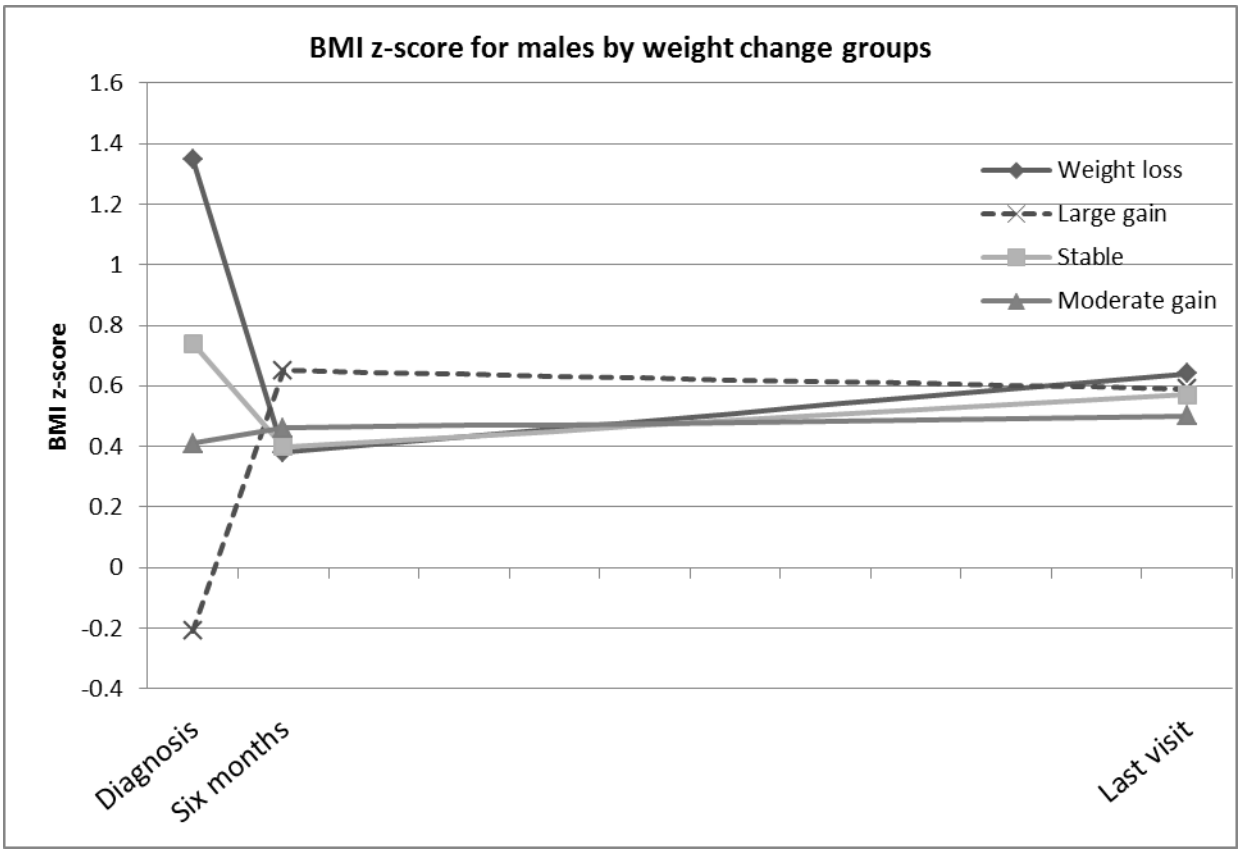


The weight loss and stable groups lost weight in the first six months, while the other two groups gained weight. Females in the weight loss group had slightly lower BMI z-score than the large gain group at six months. Between six months and the last visit, BMI z-score for the moderate gain group was stable around 0.5. BMI z-score for the stable group rose from 0.5 six months after diagnosis, to just below 0.8 at last visit. Large gainers had the highest average BMI z-scores at last visit, and the weight loss and stable groups were also near the same level, while the Moderate gain group was lower. The pattern of BMI z-score increase between six months and last appears to be parallel among three (large gain, weight loss and stable) groups.

4.5.4 Change in BMI z-score for males by weight change groups

Figure 16 shows trends of BMI z-score changes for males by weight change group.

Figure 16: Change in BMI z-score for males by weight change group

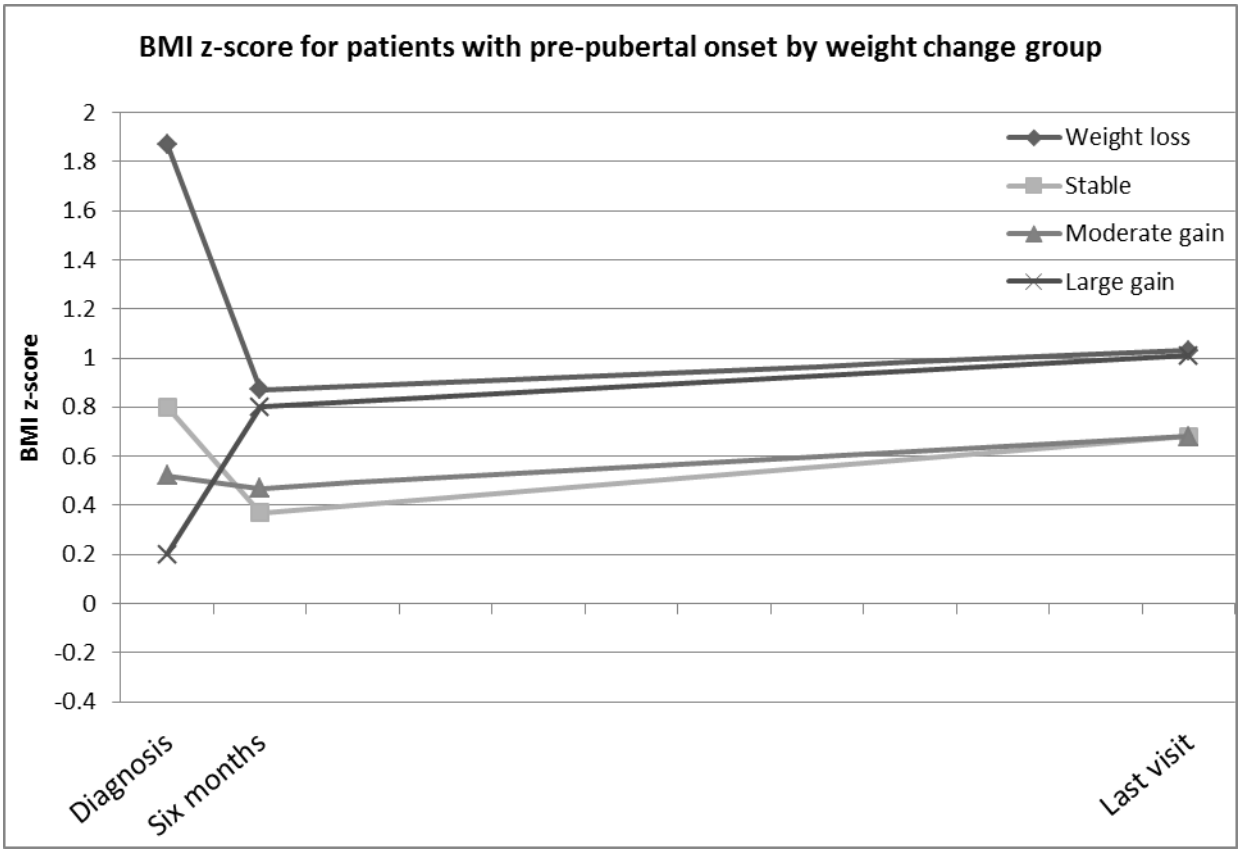


The weight loss group showed a dramatic decline in the six months after diagnosis. Their average BMI z-score at 6 months was lower than all other groups, but then they gained back some weight, and ended with the highest BMI z-scores at last visit. The average BMI z-score for the large gain group peaked at six months, and declined slightly by the last visit. The moderate gain group had a slight increase at six months, and was stable thereafter, ending with the lowest average of all four groups. As was shown for females, the groups were dramatically closer together by the last visit, though all were above the population average of 0. However, all four groups for females were above all four groups for males (group averages near 0.8 for females and 0.6 for males).

4.5.5 Change in BMI z-scores for patients with pre-pubertal onset by weight change groups

Figure 17 shows the pattern of BMI z-score changes by weight change groups for patients who were pre-pubertal at diagnosis.

Figure 17: Change in BMI z-score for patients with pre- pubertal onset by weight change group



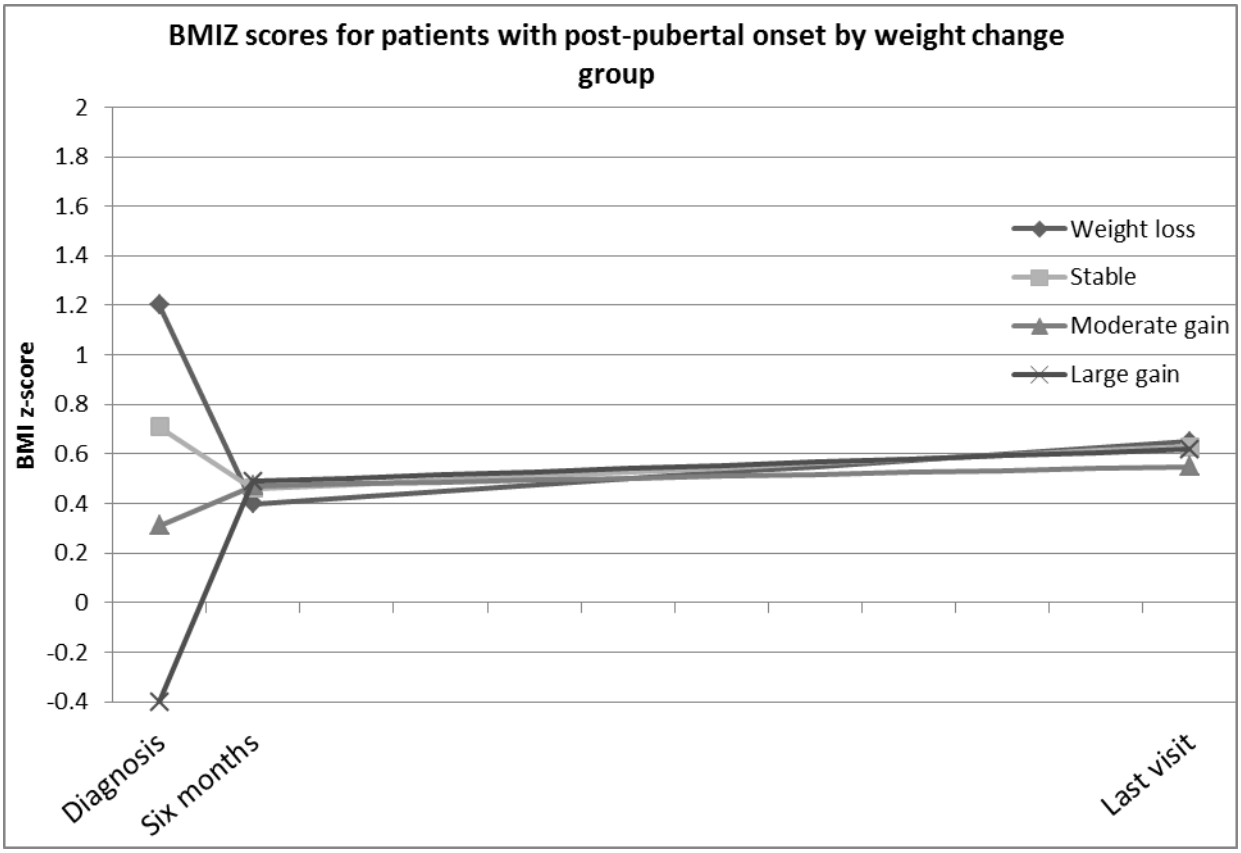
The results show that all four of the weight change groups had average BMI z-scores above zero at diagnosis. That is, among those with pre-pubertal onset, all groups had above average BMI at diagnosis. Those in the weight loss group showed a dramatic reduction in the first six months, from over 1.8 to just over 0.8 standard deviations above zero, though this was still the highest average of all groups. The large gain group started with average BMI z-score 0.2 standard deviations above zero at diagnosis and increased steadily to converge with the weight loss group at about 0.8. The BMI z-score for the stable group trended downwards from 0.8 to just below 0.4 six months after diagnosis. By the last visit, BMI z-score for this group had gone back up to where it was at diagnosis. The moderate gain group had stable and modest changes in

BMI z-score over time. There was more variability in average BMI z-scores among the four groups at the last visit than was seen in previous figures.

4.5.6 BMI z-score for patients with post-pubertal onset by weight change groups

Figure 18 shows the trajectory of changes in BMI z-scores by weight change groups for patients with post-pubertal onset of T1DM.

Figure 18: Change in BMI z-score for patients with post-pubertal onset by weight change group



The pattern of BMI z-scores over time for those with post-pubertal onset is different for all four groups compared to their pre-pubertal counterparts shown in Figure 17. The weight loss group ended with the highest BMI z-scores at last visit, but had lost enough weight at six months after diagnosis to have the lowest average BMI z-scores at that point. The average BMI z-score for the four groups was dramatically less variable at their last visit compared to pre-pubertal

patients. The trajectory of change in BMI z-scores for moderate gainers was distinctly linear, which appears to resemble the pattern for this group in all analyses.

4.6 Final analytic models

4.6.1 Introduction

The objective of the analytic modeling was to quantify the association between the outcome variable (BMI z-score at last visit) and the independent variable (change in BMI z-score from diagnosis to six months), while controlling for sex, pubertal status and BMI at diagnosis, and duration of treatment. Results from the Generalized Linear Models (GLM) including all patients are presented in Table 5. Tables 6 and 7 show results for patients with pre and post- pubertal onset, respectively. These separate models were created because the descriptive analyses revealed significantly different results and patterns for these two groups.

4.6.2 Visualizing the model results

The results from the analytic models (Tables 5-7) reveal that BMI z-score at diagnosis, patient sex, weight change group, and pubertal status were all significantly related to the outcome (in that order). To better understand the relationships of these variables to BMI z-score at last visit, a series of graphs (Figures 19-21) were made to illustrate the nature of the association between BMI z-score at diagnosis and the modelled BMI z-score at last visit by weight change group, and then separately by sex and by pubertal status. They are line graphs, showing the actual average BMI z-score for each weight change group at diagnosis, six months later, and then their modelled BMI z-score at last visit. Each of the graphs is presented after the analytic model for that group. Overall, these graphs are very similar to those shown in the descriptive results

above. This was expected, because the values at diagnosis and at six months are the same data – the only difference is that the data for BMI z-score at Last visit in this series of graphs were produced by the models, so they adjust for the other variables.

4.6.3 Results of analytic model for all patients

The results in Table 5 show the effects of each variable on the outcome (BMI z-score at last visit), after controlling for all other variables listed in the table. Statistically significant results are shown with an asterisk(s). Male sex, the large weight gain group, and follow up for longer than 10 years were selected as reference groups for the categorical variables.

Table 5: Results of Generalized Linear Models for all patients

Parameter	Model 1	Model 2	Model 3	Model 4
Intercept	0.88(0.05)	0.85(0.05)	0.71(0.06)	0.55(0.11)
BMI z-score at diagnosis	0.65(0.03)***	0.53(0.05)***	0.53(0.05)***	0.53(0.05)***
Weight change groups				
Weight loss	-1.01(0.18)***	-1.61(0.40)***	-1.62(0.38)***	-1.60(0.39)***
Stable	-0.71(0.10)***	-0.80(0.1)***	-0.77(0.11)***	-0.76(0.11)***
Moderate gain	-0.53(0.07)***	-0.53(0.72)***	-0.50(0.07)***	-0.48(0.07)***
Large gain	ref	ref	Ref	ref
Interaction terms for BMI z-score at diagnosis and weight change group				
BMIZ_0*weight loss		0.58(027)*	0.58*	0.56(0.26)*
BMIZ_0*stable		0.28(0.10)**	0.28(0.26)**	0.28(0.10)**
BMIZ_0*moderate gain		0.18(0.07)*	0.18(0.10)**	0.17(0.01)*
BMIZ_0*large gain		ref	Ref	ref
Sex				
Female			0.29(0.06)***	0.28(0.6)***
Male			Ref	ref
Duration of follow up				
0-5 years f/up				0.15(0.15)
6-10 years f/up				0.20(0.11)*
> 10 years f/up				ref
R^2	**0.52**	**0.53**	**0.56**	**0.57**
Adjusted R^2	**0.51**	**0.53**	**0.55**	**0.56**

Data in cells are parameter estimates (Standard Error); BMIZ_0: BMI z-score at diagnosis

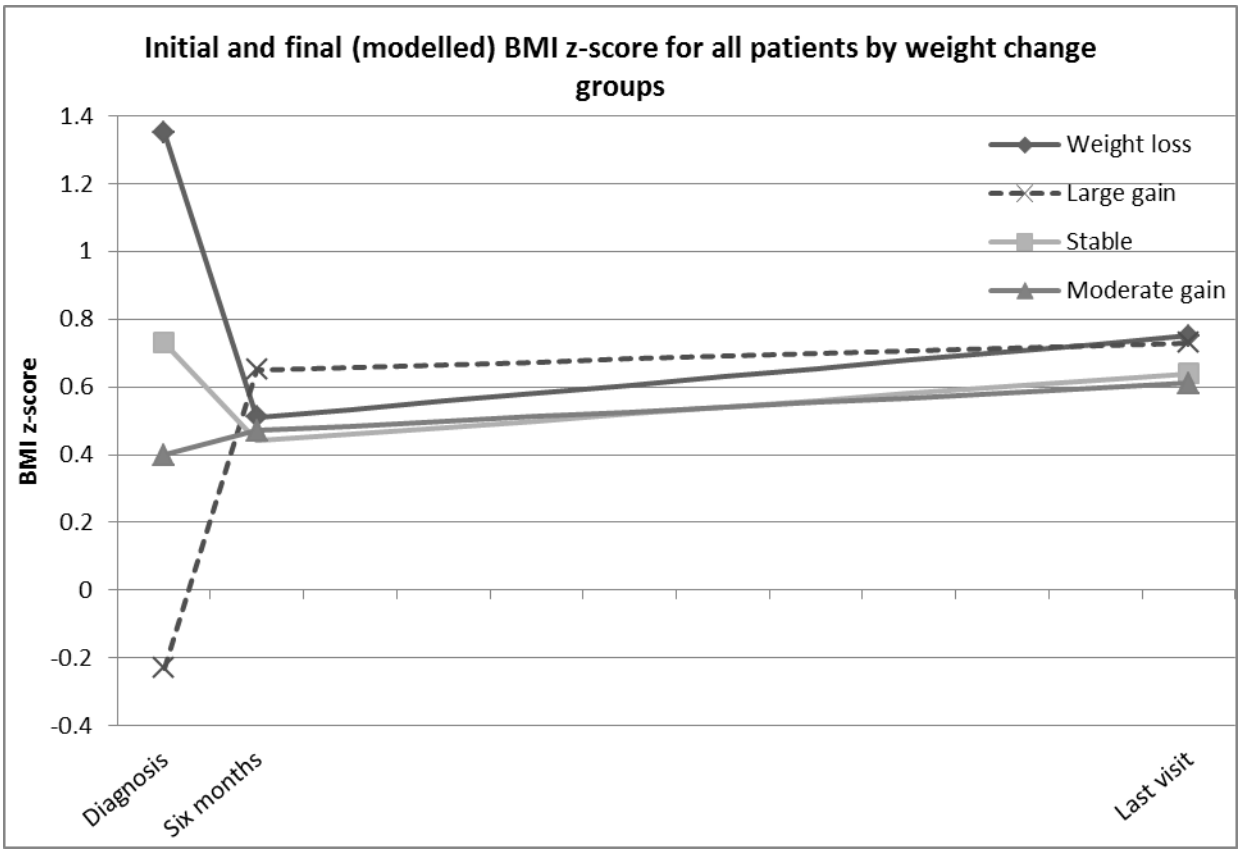
The results in Table 5 show that all independent variables used were significantly associated with the outcome (BMI z-score at last visit), and that the models were reasonably strong in

terms of variance explained (R^2 values were all above 0.5). The ranking by strength of association was: BMI z-score at diagnosis, sex, change in BMI z-score in the six months after diagnosis, the interaction term between change in BMI z-score and BMI z-score at diagnosis , and longer (>5 years) follow up. BMI z-score at diagnosis was the most significant factor; indeed, a model using just BMI z-score at diagnosis (not shown in Table 5) revealed that it alone was a strong predictor of increased BMI z-score at last visit ($R^2 = 0.41$).

Model 1 includes both BMI z-score at diagnosis and weight change group in the first six months (weight loss, stable, moderate gain, or large gain). Both variables were significantly associated with the outcome, and the R^2 value was 0.52. BMI z-score at diagnosis was positively associated with the outcome but weight change group was negatively associated. Model 2 added the interaction terms representing the combined effect of BMI z-scores at diagnosis and weight change group. The interaction terms were all significantly associated with increased BMI z-score at last visit, and the model R^2 was 0.53. The significance of the interaction terms means that the impact of the change in BMI z-score in the first six months on the outcome depends on the patient's BMI z-score at diagnosis. Model 3 added patient sex, which was also significantly associated with BMI z-score at last visit, and the R^2 increased to 0.56. Model 4, the final model, added duration of follow up, which improved the model further, but only slightly ($R^2 = 0.57$).

Figure 19 illustrates these results for all patients, incorporating the modelled BMI z-score at last visit for each patient.

Figure 19: Modelled last BMI z-score for all patients by weight change group

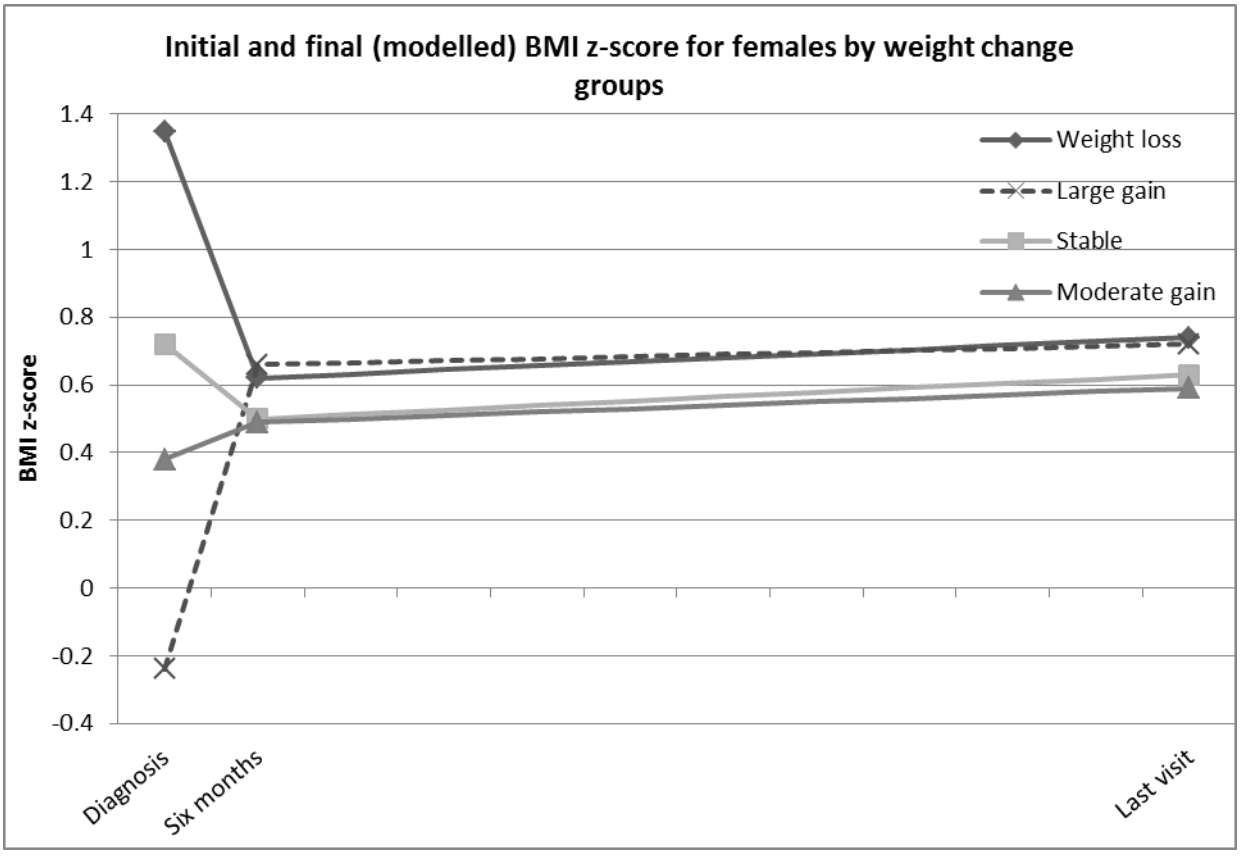


The results in Figure 19 show that the patterns of weight change in the six months after diagnosis for the large gain and weight loss groups were almost mirror images of each other. The BMI z-score for the large gain group rose rapidly, from the lowest (-0.23) among all four groups at diagnosis to highest (0.65) six months later. Those in the weight loss group were diagnosed with the highest BMI z-score (1.35), but lost weight rapidly by six months later (reaching 0.51). The BMI z-score for the stable group trended downward suggesting some weight loss in the six months after diagnosis but not to the same extent as the weight loss group. The trajectory of weight change for the moderate gain group shows an almost perfectly linear trend in BMI z-score over time. The modelled BMI z-score for all the groups show that at

last visit, T1DM patients end up with BMI z-score above zero, but much closer together than at diagnosis.

Results for females: The results from earlier analyses showed that patient sex was a significant variable, but that its effect was consistent across other sub-groups, so separate models for males and females were not required. Figure 20 illustrates the results for females, incorporating the modelled results for BMI z-score at last visit, using the main model.

Figure 20: Modelled BMI z-score at last visit for females by weight change groups

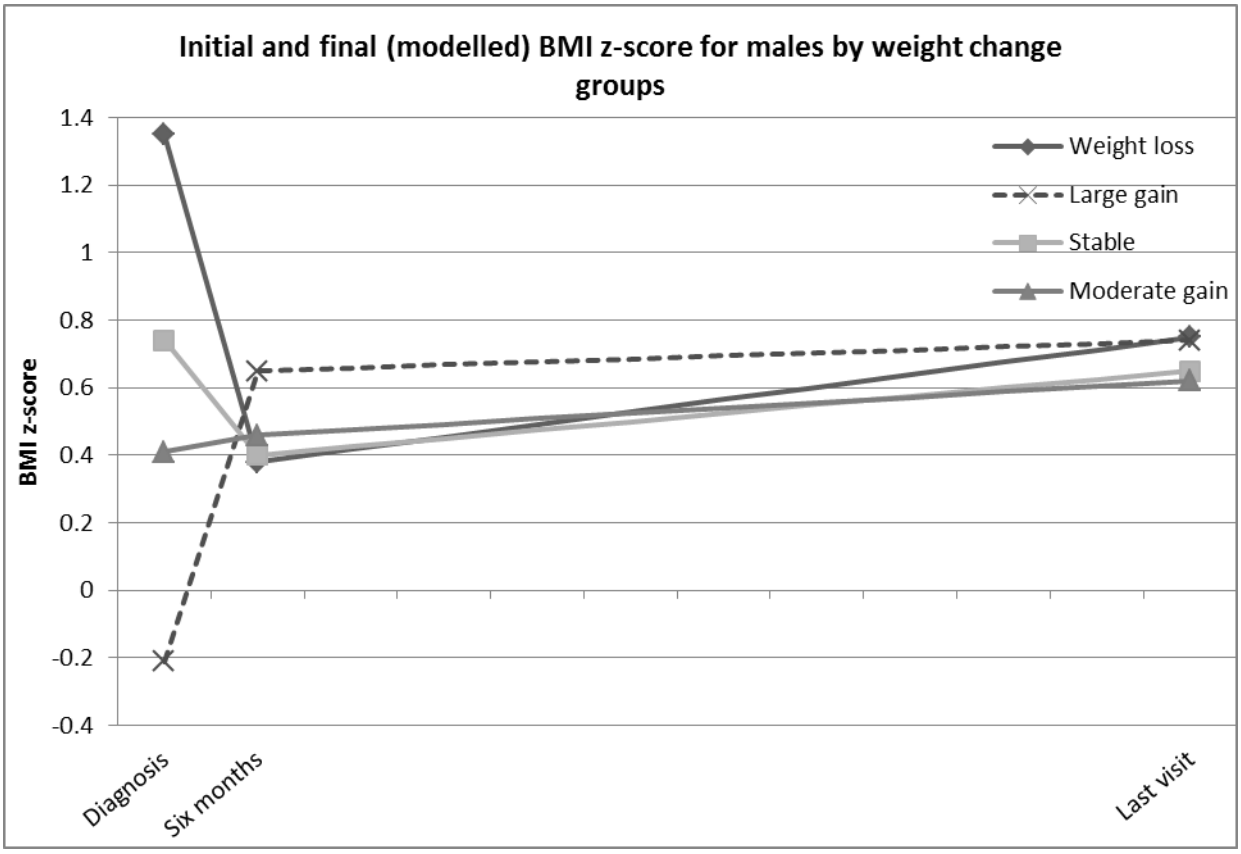


Results in Figure 20 show that all but the large gain group for females had BMI z-score above zero at diagnosis. The large gain and weight loss groups started with BMI z-score on opposite ends, and had higher BMI z-score than the stable and moderate gain groups six months later

and at last visit. Modelled BMI z-score for females show less variability among the four weight change groups at last visit than at diagnosis

Results for males: Figure 21 illustrates the results for males, incorporating the modelled results for BMI z-score at last visit.

Figure 21: Modelled BMI z-score at last visit for males by weight change group



Results in Figure 21 show that all weight change groups for males had modelled BMI z-scores closer together at last visit. The large gainers had the highest BMI z-score six months after diagnosis than the other three groups with BMI z-scores that appear to be much closer together. At last visit, the Stable and moderate groups had slightly lower BMI z-scores than the large gainers and those in the weight loss groups. The pattern of modelled BMI z-scores for

males resembled that of females with large weight gain and weight loss groups closer together and higher than the other two groups at last visit.

4.6.4 Results of analytic models for patients with pre- pubertal onset of T1DM

The results in Table 6 show the effects of each independent variable on BMI z-score at last visit for patients with pre-pubertal onset of T1DM.

Table 6: Results of Generalized Linear Models for patients with pre-pubertal onset of T1DM

Parameter	Model 1	Model 2	Model 3	Model 4
Intercept	0.89(0.10)	0.90(0.11)	0.72(0.11)	0.53(0.15)
BMI z-score at diagnosis	0.57(0.06)***	0.51(0.09)***	0.54(0.09)***	0.57(0,09)***
Weight change groups				
Weight loss	-1.05(0.39)**	-3.24(1.57)*	-3.04(1.49)*	-3.08(1.48)*
Stable	-0.56(0.20)**	-0.51(0.28)	-0.56(0.27)*	-0.53(0.27)*
Moderate gain	-0.57(0.13)***	-0.60(0.14)***	-0.55(0.13)***	-0.51(0.13)***
Large gain	ref	ref	ref	Ref
Interaction terms for BMI z-score at diagnosis and weight change group				
BMIZ_0*weight loss		1.23(0.82)	1.04(0.78)	1.01(0.77)
BMIZ_0*stable		-0.01(0.28)	0.04(0.26)	0.02(0.26)
BMIZ_0*moderate gain		0.10(0.13)	0.06(0.12)	0.028(0.12)
BMIZ_0*large gain		ref	ref	Ref
Sex				
Female			0.41(0.11)***	0.42(0.11)***
Male			ref	Ref
Duration of follow up				
0-5 years f/up				-
6-10 years f/up				0.23(0.12)*
> 10 years f/up				Ref
R^2	**0.45**	**0.46**	**0.51**	**0.53**
Adjusted R^2	**0.43**	**0.42**	**0.47**	**0.47**

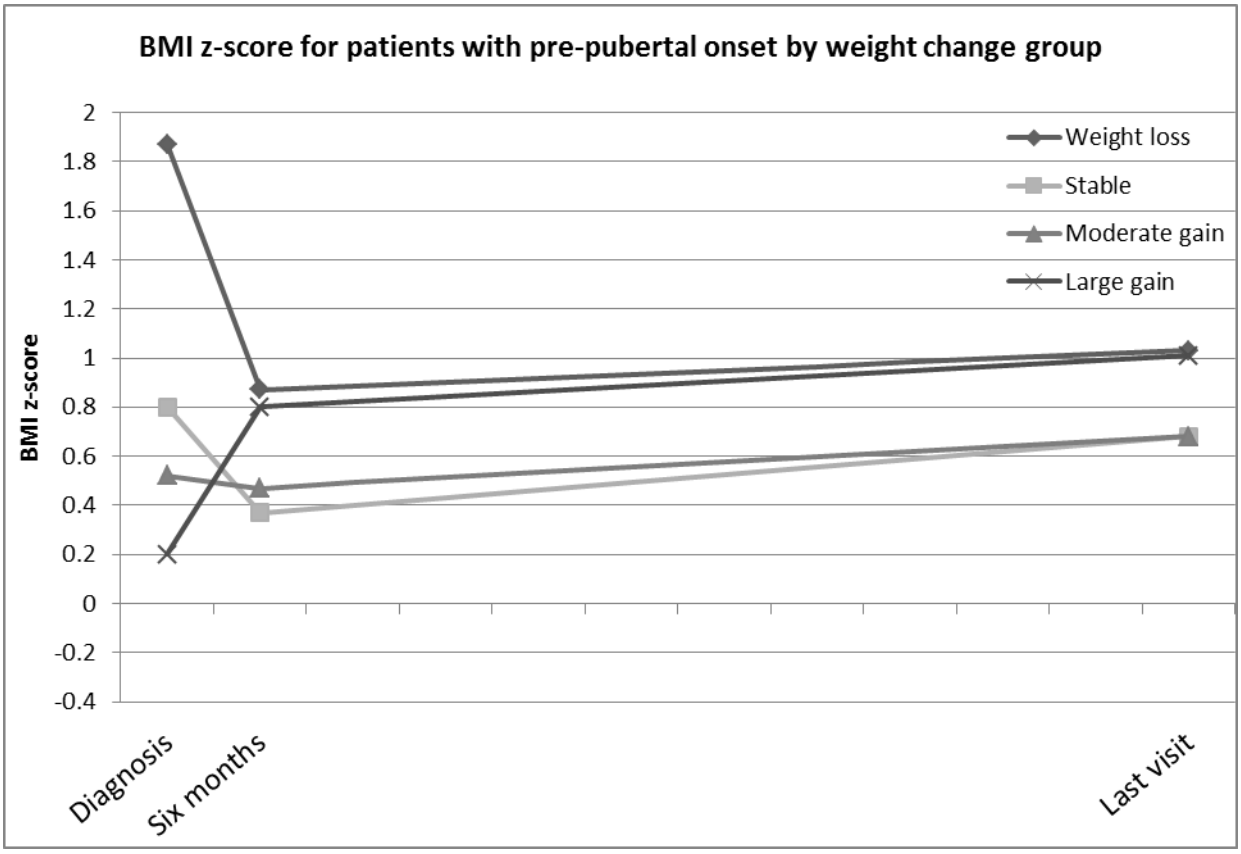
Data in cells are parameter estimates (Standard Error); BMIZ_0: BMI z-score at diagnosis

Ranked by strength of association, the results show that BMI z-score at diagnosis, sex, and change in BMI z-scores in the six months after diagnosis were significantly associated with the outcome. For patients with pre-pubertal onset, the interaction terms between BMI z-score at diagnosis and the change in BMI z-scores six months later were not significantly associated with the outcome (BMI z-score at last visit).

Model 1 included BMI z-score at diagnosis and weight change group in the six months after diagnosis. Both variables were significantly associated with the outcome and the R^2 value was 0.45. Model 2 added the interaction term showing combined effects of BMI z-scores at diagnosis and weight change group. The interaction terms were not significantly associated with the outcome, and the R^2 increased only slightly to 0.46. Patient sex was added in Model 3, and was significantly associated with the outcome, increasing the R^2 value to 0.51. Model 4 added duration of follow up, which was not significantly associated with the outcome and the R^2 increased to 0.53.

Figure 22 illustrates the results for those with pre-pubertal onset of T1DM, incorporating the modelled results for BMI z-score at last visit.

Figure 22: Modelled last BMI z-score for patients with pre-pubertal onset by weight change group



Results in Figure 22 show that for those with pre-pubertal onset of T1DM, the average BMI z-score for all four weight change groups were above average at diagnosis. By six months after diagnosis, the BMI z-score for the large gain and weight loss groups were close to 0.80, while the stable and moderate weight gain groups were around 0.4. These pairs of groups also have similar trends from 6 months to their last visit: the large gain and weight loss groups' modelled BMI z-score at last visit were close together and higher than those of the other two groups. For all four groups, the average modeled BMI z-score at last visit was above zero, as was shown for all patients in Figure 19.

4.6.5 Results of the analytic model for patients with post-pubertal onset of T1DM

Results of the regression models for patients diagnosed after puberty are presented in Table 7.

Table 7: Results of Generalized Linear Models for patients with post-pubertal onset of T1DM

Variable	Model 1	Model 2	Model 3	Model 4
Intercept	0.90(0.06)	0.83(0.06)	0.71(0.07)	0.79().11)
BMI z-score at diagnosis	0.69(0.04)***	0.52(0.06)***	0.51(0.06)***	0.50(0.06)***
Weight change groups				
Weight loss	-1.03(0.20)***	-1.63(0.41)***	-1.67(0.41)***	-1.64(0.41)***
Stable	-0.79(0.11)***	-0.84(0.12)***	-0.80(0.12)***	-0.79(0.12)***
Moderate gain	-0.52(0.09)***	-0.47(0.09)***	-0.45(0.08)***	-0.44(0.08)***
Large gain	ref	ref	ref	ref
Interaction terms for BMI z-score at diagnosis and weight change groups				
BMIZ_0*weight loss		0.73(0.32)*	0.78(0.31)*	0.77(0.31)*
BMIZ_0*stable		0.34(0.11)**	0.34(0.11)**	0.35(0.11)**
BMIZ_0*moderate gain		0.25(0.08)**	0.27(0.08)**	0.28(0.08)**
BMIZ_0*large gain		ref	ref	ref
Sex				
Female			0.23(0.07)**	0.21(0.07)**
Male			ref	ref
Duration of follow up				
0-5 years f/up				-0.09(0.09)
6-10 years f/up				ref
> 10 years f/up				-
R^2	**0.56**	**0.59**	**0.61**	**0.61**
Adjusted R^2	**0.55**	**0.58**	**0.60**	**0.59**

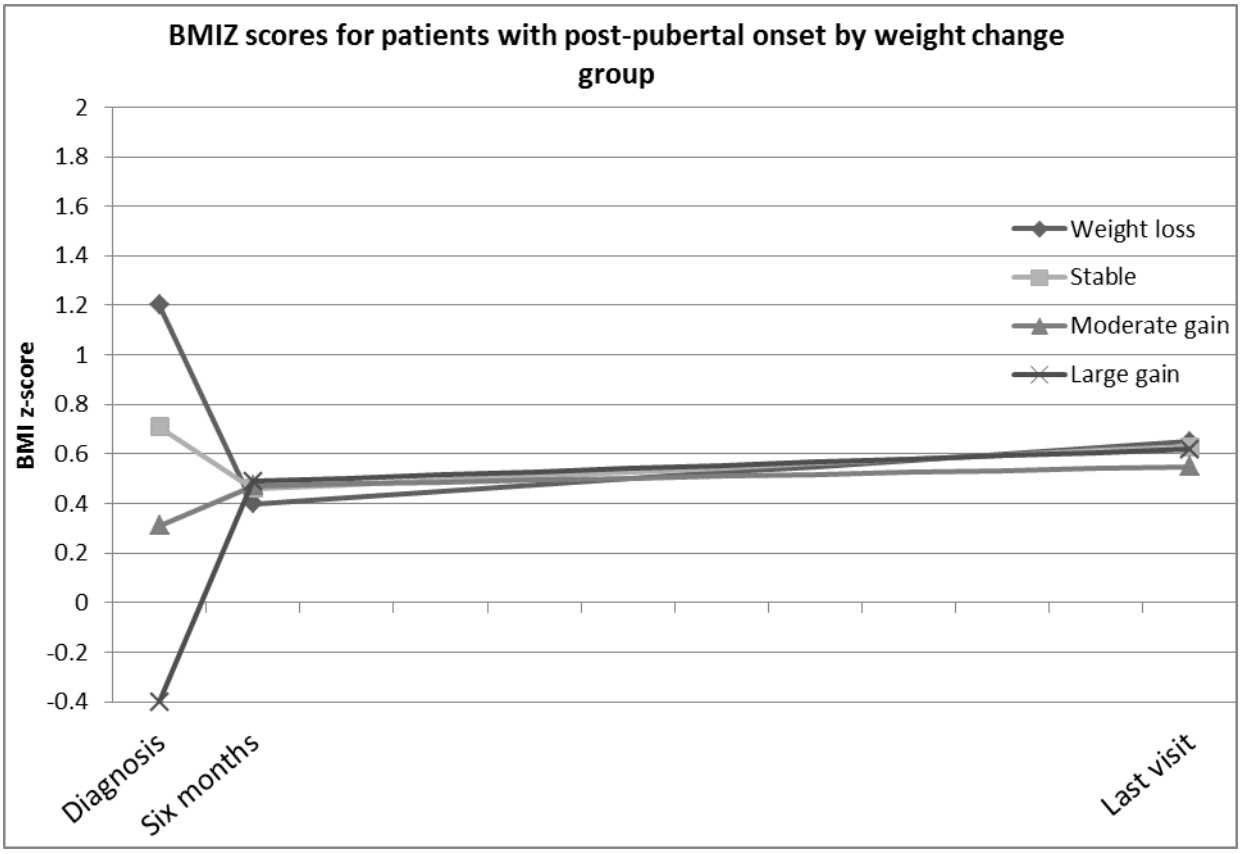
Data in cells are parameter estimates (Standard Error); BMIZ_0: BMI z-score at diagnosis

The results show that most of the independent variables used were significantly associated with BMI z-scores at last visit. Duration of follow up was the only variable not significantly associated with the outcome for patients diagnosed after puberty. The ranking by strength of association was: BMI z-score at diagnosis, weight change group, sex, and the interaction terms between BMI z-score at diagnosis and weight change group. A model using just BMI z-score at diagnosis (not shown in table 7) demonstrated that it alone was a strong predictor of increased BMI z-score at last visit (R^2 = 0.44).

Model 1 included BMI z-score at diagnosis and weight change group, which were both significantly associated with BMI z-scores at last visit. Model 1 had an R^2 value of 0.56. Model 2 added the interaction between BMI z-score at diagnosis and weight change group, all of which were significantly associated with BMI z-score at last visit. Adding the interaction terms increased the R^2 to 0.59. Model 3 added patient sex, which was also significantly associated with the increased BMI z-score at last visit, and increased the model R^2 to 0.61. Model 4 added Duration of follow up, which was not significantly associated with the outcome, and did not increase the R2 value.

Figure 23 illustrates the results for those diagnosed after puberty, incorporating the modelled results for BMI z-score at last visit

Figure 23: Modelled last BMI z-score for patients with post-pubertal onset by weight change group



Results in Figure 23 show that for patients diagnosed after puberty, BMI z-score for the four groups were very disparate at diagnosis, but very close together six months later, and even closer at last visit. Unlike their pre-pubertal counterparts, BMI z-score for these patients rose (but not much) from around 0.45 at six months after diagnosis to about 0.65 at last visit for all groups.

4.6.6 Summary of results

Only 9% of the patients in this study were underweight at diagnosis, but 15% were overweight and 8% were obese. Once diagnosed and insulin therapy was initiated, most (91%) but not all patients in this study cohort gained weight. The change in weight was rapid, but varied based

on individuals' initial BMI z-score, sex, and pubertal status. On average, patients who had lower BMI z-score at diagnosis gained the most weight, while those at higher BMI z-score either lost weight or remained relatively unchanged over the first six months after diagnosis. At last visit, 26% of the patients were overweight and 9% were obese while only 2% were underweight. A higher proportion of females (33%) were overweight at the last visit compared to males (20%). More males (10%) were obese than females (7%) at last visit. Females had significantly higher BMI z-score (0.82 ± 0.68) than males (0.54 ± 0.93) at age 18. BMI z-score at diagnosis, Female sex, weight change group, interaction term between BMI z-score at diagnosis and weight change group, and longer (>5 year) duration of follow up were significantly associated with higher BMI z-score at last visit. The effects of BMI z-score at diagnosis were mediated by the magnitude of weight change in the six months after initiation of insulin, which was the most significant predictor of higher BMI z-scores at last visit. The effects of other variables (age, presence or absence of DKA, year and period of referral) on BMI z-score at last visit were assessed. None of them were significantly associated with the outcome and analyses showing relationships of these variables to the outcome are not presented in this study.

Chapter 5: Discussion

5.1 Introduction

This study adds to the growing body of literature in the area of obesity among children and adolescents diagnosed with T1DM. With the incidence and prevalence of obesity and T1DM concurrently increasing among children and adolescents, there has been debate among clinicians and researchers about how the two conditions are or are not related. This chapter highlights and discusses specific findings of this study and how they relate to previous literature and provide insights into potential future clinical and policy decisions.

Results from this study show very large variations in BMI z-score at diagnosis and different weight change trajectories among sub-groups. Previous research[35,36,48,123] and clinical experience suggest that most children and adolescents have a negative BMI z-score when diagnosed with T1DM, and gain weight after the initiation of insulin therapy. The results of this study show that BMI z-scores at diagnosis vary greatly across sub-groups, but become relatively similar within 6 months of treatment.

This study also shows that at their last visit to the DER-CA clinic prior to transfer to adult care (age 16-18); all patients had BMI z-scores well above zero. This is concerning because there is no clinically relevant reason why they should have higher than average BMI z-scores. No published studies have evaluated the potential long-term effects of insulin-induced weight gain among children and adolescents with T1DM. Furthermore, previous studies evaluating weight change among T1DM children and adolescents have not assessed these changes by BMI groups at diagnosis and magnitude of weight change, as was done in this study. This approach provides

a more accurate understanding of various patterns of BMI change, accounting for important differences that exist among distinct subgroups.

5.2 BMI z-scores and BMI group membership at diagnosis

The most unexpected and yet clinically important finding in this study is that only 9% of new T1DM patients were underweight at diagnosis. Unexplained loss of weight, which can lead to underweight, is one of the classical presentations of T1DM, and a common criterion for diagnosis. Due to weight loss prior to T1DM diagnosis, most clinicians believe that a significant number of children and adolescents will be underweight at diagnosis. The rates of underweight in this study were above the national average[198], but much lower than expected by clinicians. Early detection and diagnosis of T1DM before individuals lose enough weight to be classified underweight may be responsible for the low prevalence of underweight patients found here. Alternatively, the use of CDC cut-offs for defining BMI groups may have resulted in the underestimation of underweight and perhaps overestimating the other BMI groups. It has been previously reported[149,198] that different (WHO, CDC and IOTF) cut-offs for defining BMI groups may result in different prevalence estimates. de Onis and others reported that the CDC growth charts underestimated under-nutrition compared to the WHO growth charts[199]. Schwarz et al reported similar results in a much younger (0-15 month old) group of Gabonese children[200].

The fact that 15% were overweight and 8% obese at diagnosis indicates, as has been reported[17,19], that many patients' BMI z-scores were high prior to T1DM diagnosis. This study found no significant differences in BMI z-scores at diagnosis between males and females, although females tended to have lower BMI z-scores than males (0.23 vs. 0.31). These results

are similar to those reported by Frohlich-Reiterer and associates whose study showed that males (0.23) had higher BMI z-scores than females (0.15) at diagnosis, although they did not report if the difference was statistically significant[123]. Davis et al found females to be significantly leaner than males at diagnosis and a year later[36]. The fact that females were significantly leaner than males at diagnosis may help to explain their findings one year later, since BMI z-score at diagnosis, as shown in this study, was associated with BMI z-score at last visit. Libman and associates found that children and adolescents diagnosed with T1DM had equal or higher initial BMI z-scores than controls[18].

Although the baseline overweight and obesity rates in this study were lower than the national[198] and provincial[201,202] averages, these results show that a significant number of children and adolescents being diagnosed with T1DM are presenting in overweight or obese states. This may be a reflection of the generally high and increasing overweight and obesity rates among the population over the past decades[47]. Alternatively, these findings may give credence to the disputed "accelerator" hypothesis, which argues that childhood overweight and obesity contributes to T1DM incidence[22]. The accelerator hypothesis of Wilkin et al., posits that T1DM and T2DM are similar, distinguishable only by their rate of beta cell destruction[203]. Newfield and associates did not report on underweight at diagnosis, but they found prevalence of overweight (14.6%) and obesity (7.7%) comparable to those found here[35].

Results from this study also show that average BMI z-scores at diagnosis were significantly higher for patients diagnosed before puberty than for those diagnosed after puberty. This finding differs from the results reported by de Vries et al who found no significant difference in

BMI z-scores between pre and post pubertal patients with T1DM at diagnosis[120]. A plausible explanation for this difference may be that in this study, a higher proportion of those diagnosed before puberty were males, and males tended have higher BMI z-scores at diagnosis than females.

5.3 Post diagnosis weight change

Results from this study indicate that six months after initiating insulin therapy, most T1DM patients gained weight. Three studies showed similar results which demonstrated that weight gain after T1DM occurs rapidly[35,36,120]. The mean BMI z-score of 0.53 for the cohort at six months was similar to the mean BMI z-score of 0.4 reported by de Vries et al[120]., but lower than the 0.7 reported by Dabelea et al. in the SEARCH study,[204] and the 0.86 reported by Newfield et al[35]. This variation may be partially explained by the differences in measurement periods. In the SEARCH study, Dabelea and associates measured BMI z-scores between three and twelve months after diagnosis[204], while Newfield and others reported BMI z-scores 4.5 – 7 months after diagnosis[35]. Additionally, we included the underweight category which Newfield et al did not include and this may have contributed to the lower average BMI z-scores at six months in this study[35].

Most of the weight gain occurred rapidly, within weeks of diagnosis, as has been reported previously. However, the trend of weight gain was different for each of the four baseline BMI groups. As expected, patients in the underweight BMI group at diagnosis gained the most weight, followed by those in the normal weight group. Previous studies have noted rehydration[36], replenishment of lost fat[120], and possible anabolic effects of insulin as possible

reasons for weight gain. However, not all patients gained weight: those in the overweight or obese groups at diagnosis lost weight during the first six months, though many subsequently re-gained some of that weight. Overall, 9% of patients in this study cohort lost weight during the six months after diagnosis. Contact with health care professionals and education about healthy behaviours, food consumption, and physical activity may have contributed to weight loss. Being diagnosed with T1DM and the care surrounding it, resulted in dramatically less variability in BMI z-scores by six months after diagnosis. Just as patients who were diagnosed with higher BMI z-scores lost weight, those with lower BMI z-scores at diagnosis gained weight. The result was a convergence of BMI z-scores, with those starting at higher values being above average BMI z-scores at six months as well. Previous studies did not assess the post diagnosis weight change by these subgroups. This study was the first to analyse post-diagnosis weight gain by initial weight status and 6-month weight change groups. Newfield and associates only looked at overall weight gain over 4-7 months after diagnosis[35]; de Vries et al compared males and females over time[120], and so did Davis and associates, at 6 weeks and one year later[36].

As expected, while weight gain occurred, the underweight category dropped from 9% to only 2% by six months after diagnosis. The normal weight group (still the largest six months after diagnosis) was relatively unchanged at 68-70%. Overweight rose from 15 to 21%, while the obese group remained relatively unchanged at 8-9%. These findings are comparable to those reported by Newfield et al who also found higher overweight rates at six months after diagnosis[35]. The majority of patients from the underweight category moved to normal weight

and a significant portion of those beginning in the normal weight category became overweight. Females contributed more than males to the movement from normal weight to overweight.

The increase in the overweight category suggests that some individuals who started in the normal weight category gained enough weight to move to this category, though a small percentage from the obese group lost weight and also joined the overweight group. As mentioned above, by evaluating weight change by categories, this study was able to demonstrate that not all individuals follow the same pattern of weight change; hence results of this study show that obesity actually went down by 1% unlike the steady increase as reported by Newfield and associates[35].

Results of this study show that BMI z-score at diagnosis was the strongest predictor of BMI z-score at last visit, but that its effect was mediated by weight change in the six months after diagnosis. Interestingly, this effect was different for those diagnosed before puberty than after puberty. For patients diagnosed before puberty, the interaction term between BMI z-score at diagnosis and weight change group was not significantly associated with the outcome. This means that for those diagnosed before puberty, the impact of BMI z-score at diagnosis on BMI z-score at last visit was not mediated by weight change in the first six months. However, the interaction was significant for those diagnosed after puberty, such that the effects of higher BMI z-scores at diagnosis were particularly strong for those in the weight loss group. The average BMI z-score for patients diagnosed after puberty and categorized in the weight loss group at six months was 1.3 standard deviations above zero at last visit.

Given that duration of follow-up was significantly related to the outcome, and average follow-up duration is longer for those diagnosed before puberty, one might be tempted to speculate that at least some portion of the pre- vs. post-puberty differences noted are related to this difference in follow-up duration. However, the results clearly show, for both groups, that most of the change in BMI z-scores occurs shortly after diagnosis, as has been previously demonstrated[35,36].

5.4 BMI z-score and BMI group membership at last visit

Overall, patients in this study cohort had BMI z-scores well above zero at their last visit to the DER-CA clinic, confirming anecdotal evidence and concerns by DER-CA clinicians who observed that their patients appeared heavier than expected at the time of transition to adult care. At last visit, females in the study cohort had significantly higher BMI z-scores than males, though both were above average. These results are consistent with those of de Vries and others who found females to have higher BMI z-score than males six years after diagnosis[120]. Domargard et al found higher BMI z-scores among post pubertal females than males[118]. A recent study by Frohlich et al also found female sex to be a significant predictor of increased BMI z-scores for adolescents with T1DM[123].All these results are in contrast to the findings of a study of adults with T1DM by Conway et al., which did not find significant sex differences in BMI after 18 years of follow up[103].

The sex differences in BMI z-scores at last visit for this study cohort could be explained by physiological, treatment and lifestyle factors. McCarthy et al reported that females gain more

fat mass throughout life than males, most markedly at puberty, predisposing them to higher adiposity later in life[192]. Dunger et al suggested that sex hormones in females may contribute to higher their BMI z-score, and subsequent intensification of insulin therapy with resultant elevated leptin levels[191]. Elevated leptin is associated with more gains in fat mass among females and not males[205]. Murphy et al [38] suggested that the influence of sex-linked genes intrinsically predisposes pre-pubertal females to insulin resistance thus they may require higher insulin doses and intensive insulin therapy, which both have been independently linked to higher BMI z-score[122]. Due to the secondary nature of our study, we could not assess lifestyle factors; however eating habits[206] and physical activity[207], which can both independently affect BMI z-score, may be different between males and females.

At last visit, the proportion of overweight was significantly higher for females than males. Obesity was slightly more prevalent among males, though the difference was not statistically significant. de Vries et al reported comparable results, observing increases in overweight and obesity rates over six years among their cohort, with no significant sex differences in the rates[120]. However, results of this study show higher overweight (26%) and obesity (9%) rates than in the study by de Vries and others which showed 15.6% overweight and 6.5% obesity rates among their cohort. Because both studies used the CDC growth chart cut-offs for estimates, the difference may be attributed to duration of follow up, this study being longer[121]. At last visit, prevalence of overweight (33%) but not obesity (7%) for females in the study cohort was higher than national[198] and provincial[201] estimates. But the corresponding rates at diagnosis were both lower than the national and provincial estimates. Therefore BMI z-score at

diagnosis alone cannot be responsible for the significantly higher overweight prevalence at last visit. A possible explanation for the difference may be weight gain associated with insulin therapy among females in this study. Previous research has reported higher rates of resistance to insulin among females[38]. Resistance to insulin may have resulted in change of treatment regimen to intensive insulin therapy, which is known to cause more weight gain.

5.5 Effects of initial BMI z-scores on obesity at 18

The results of this study show that most but not all patients gained weight rapidly after diagnosis, likely related to the initiation of insulin. However, results of this study also show that the most important predictor of higher BMI z-scores at last visit was a patient's BMI z-score at diagnosis. Patients with higher BMI z-scores at diagnosis were more likely to have higher BMI z-score at the last visit than those with lower initial BMI z-score. This finding is consistent with results from previous studies which reported that overweight and especially obesity tracks from childhood to early adulthood[43,45]. Conway and associates demonstrated that for adults with T1DM, baseline BMI was a significant predictor of increased BMI 18 years later[103]. Frohlich-Reiter et al showed that initial BMI z-score was an independent predictor of weight gain during the course of diabetes[122]. Individuals with lower BMI z-score at diagnosis gained the most weight in the period following diagnosis. In addition to finding that initial BMI z-score independently predicted longer term BMI z-score, we were also able to show that magnitude of weight change in the first six months significantly moderated this effect.

Most patients who lost more than 5% of their baseline weight in the six months after diagnosis (i.e. the Weight loss group) were overweight or obese at diagnosis. As discussed above, weight

loss in the first six months may be attributed to contact with health practitioners who would have encouraged better dietary and physical activity behaviors, In addition, the patient's insulin regimen may be relevant, because patients receiving intensive insulin therapy often receive insulin analogues (e.g. insulin detemir) that are known to have appetite-suppressing side effects[100]. This could make this group more likely to lose weight than those not receiving intensive insulin therapy. Previous studies for T2DM patients have reported that obese patients on insulin detemir benefited most from its weight-gain sparing effects compared to controls[208,209]. Results of this study show that patients who lost weight mostly did so after the first few months, peaking at about six months on insulin, but regained some of the weight over time. This trend may be explained by similar observations in secular trends for weight loss programs which show lack of long term sustainability. A recent randomized controlled study among severely obese Dutch children and adolescents concluded that post treatment weight loss was not sustainable 12 months after program initiation[216].

5.6 Strengths

The major strengths of this study are its comprehensiveness and longitudinal nature, using data from the only T1DM referral centre in Manitoba, resulting in almost no potential for selection bias. The use of the longitudinal clinical database with virtually universal coverage of all cases ensures the representativeness of our study population. The data were analysed using sub-groups that were identified after exhaustive exploratory analysis to identify potential variations in trends of weight change among the cohort. These analyses provide a better understanding and consequently more accurate representation of changes in weight over time among the cohort. Furthermore, measured (not self-reported) heights and weights to calculate accurate

BMI z-score, adjusted for sex and age. Finally, this is the first study to describe BMI group membership at T1DM diagnosis and include all patients regardless of initial BMI. Most previous studies excluded the underweight group altogether and the results here show how different they are from the other groups, highlighting the benefit of including them and reporting their results separately.

5.7 Limitations

The most important limitation of this study is the potential confounding effect of missing data. Though complete and longitudinal, the DER-CA data system does not include important variables known to independently impact BMI, including adherence to insulin therapy, food consumption patterns, and activity levels, among others. The secondary use of clinical data also has inherent limitations including the potential for data collection and recording errors. Also, due to variability in exact scheduling of clinical visits, points of interest at 6 months after diagnosis and last visit had to be generated using reasonable ranges rather than exact dates. Using ranges meant that BMI measurements collected at different times were treated as having been collected at a single point in time. Finally, like all research studies, this analysis may be affected by the influence of unmeasured confounders. In developing the project, every effort was made to include relevant variables, though several had to be excluded because of incompleteness of entries in the data system.

5.8 Significance and Implications

Results of this study show that at diagnosis of T1DM, 9% of children were underweight,68% normal weight, 15% overweight, and 8% obese. This is contrary to traditional clinical teaching and expectations, which suggest that the majority of children are at low BMI when diagnosed.

Moreover, while most patients gain weight in the six months after diagnosis, those who were overweight or obese at diagnosis did not – indeed, the obese lost weight. These findings are important for clinicians to note, because it is important to monitor children's weight status, particularly in the first 6 months after diagnosis. Patients who were underweight or in the lower part of the normal range at diagnosis should be expected to gain a significant amount of weight, bringing them closer to the mean. Conversely, those obese or overweight at diagnosis should be expected to lose some weight. These groups are particularly important since this study shows that BMI z-score at diagnosis has significant implications for increased BMI z-score at 18. High overweight and obesity rates at last visit may increase the risk for cardiovascular disease for these (already predisposed) T1DM patients.

Clinicians may need to not only focus on the post-diagnosis period, but monitor patients over time to prevent or reduce the significantly high overweight and obesity rates at age 18, especially among females. Results of this study also show that the magnitude of weight change differs among different sub-groups and that the pattern of overall longer term weight status is mediated by some of these factors – most notably weight change in the first six months, sex, and pubertal status at diagnosis. Factors such as these can help identify previously unknown high-risk groups which may benefit from extra clinical attention and monitoring. Further research may be needed to examine more closely and describe in more detail the characteristics of the patients who present as overweight or obese.

The fact that post-diagnosis weight gain is not the most important predictor of longer term obesity is also important for clinicians to highlight with their patients and parents. It has been noted previously that fear of insulin-induced weight gain immediately after diagnosis may interfere with adherence to treatment[100]. If diabetic education incorporates a discussion about the risk factors for longer term obesity, this may address weight gain fears among newly diagnosed youth, and consequently may improve adherence to therapy.

References

1. Canadian Diabetes Association. Clinical Practice Guidelines. *Canadian Journal of Diabetes.* 2013; 37(1).

2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes care.* 2008; 31 Suppl 1:S55-60.

3. Canadian Diabetes Association. An economic tsunami: The cost of diabetes in Canada. 2009.

4. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic medicine.* 1998; 15(7): 539-553.

5. International Federation of Diabetes. IDF Diabetes Atlas, 6th edition. 2013.

6. Pelletier C, Dai S, Roberts KC, Bienek A, Onysko J, Pelletier L. Report summary. Diabetes in Canada: facts and figures from a public health perspective. *Chronic diseases and injuries in Canada.* 2012; 33(1): 53-54.

7. Government of Canada (PHAC). Diabetes in Canada: Facts and Figures from a Public Health Perspective. 2011.

8. DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. *Diabetic medicine.* 2006; 23(8): 857-866.

9. Cooke DW, Plotnick L. Type 1 diabetes mellitus in pediatrics. *Pediatrics in review / American Academy of Pediatrics.* 2008; 29(11): 374-384.

10. Sherwin R, Jastreboff AM. Year in diabetes 2012: The diabetes tsunami. *The Journal of clinical endocrinology and metabolism.* 2012; 97(12): 4293-4301.

11. Patterson C, Guariguata L, Dahlquist G, Soltesz G, Ogle G, Silink M. Diabetes in the young - a global view and worldwide estimates of numbers of children with type 1 diabetes. *Diabetes Res Clin Pract.* 2014; 103(2): 161-175.

12. Tran F, Stone M, Huang CY, Lloyd M, Woodhead HJ, Elliott KD, Crock PA, Howard NJ, Craig ME. Population-based incidence of diabetes in Australian youth aged 10-18 yr: increase in type 1 diabetes but not type 2 diabetes. *Pediatric Diabetes.* 2014. doi: 10.1111/pedi.12131.

13. Long AE, Gillespie KM, Rokni S, Bingley PJ, Williams AJ. Rising incidence of type 1 diabetes is associated with altered immunophenotype at diagnosis. *Diabetes.* 2012; 61(3): 683-686.

14. Harjutsalo V, Sund R, Knip M, Groop PH. Incidence of type 1 diabetes in Finland. *JAMA : the journal of the American Medical Association.* 2013; 310(4): 427-428.

15. Skrivarhaug T, Stene LC, Drivvoll AK, Strom H, Joner G. Incidence of type 1 diabetes in Norway among children aged 0-14 years between 1989 and 2012: has the incidence stopped rising? Results from the Norwegian Childhood Diabetes Registry. *Diabetologia.* 2014; 57(1): 57-62.

16. Berhan Y, Waernbaum I, Lind T, Mollsten A, Dahlquist G. Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden. *Diabetes.* 2011; 60(2): 577-581.

17. Betts P, Mulligan J, Ward P, Smith B, Wilkin T. Increasing body weight predicts the earlier onset of insulin-dependant diabetes in childhood: testing the 'accelerator hypothesis'. *Diabetic medicine.* 2005; 22(2): 144-151.

18. Libman IM, Pietropaolo M, Arslanian SA, LaPorte RE, Becker DJ. Changing prevalence of overweight children and adolescents at onset of insulin-treated diabetes. *Diabetes care.* 2003; 26(10): 2871-2875.

19. Johansson C, Samuelsson U, Ludvigsson J. A high weight gain early in life is associated with an increased risk of type 1 (insulin-dependent) diabetes mellitus. *Diabetologia.* 1994; 37(1): 91-94.

20. Bruining GJ. Association between infant growth before onset of juvenile type-1 diabetes and autoantibodies to IA-2. Netherlands Kolibrie study group of childhood diabetes. *Lancet.* 2000; 356(9230): 655-656.

21. Hypponen E, Virtanen SM, Kenward MG, Knip M, Akerblom HK. Obesity, increased linear growth, and risk of type 1 diabetes in children. *Diabetes care.* 2000; 23(12): 1755-1760.

22. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetologia.* 2001; 44(7): 914-922.

23. Cederholm J, Eliasson B, Zethelius B, Eeg-Olofsson K, Gudbjornsdottir S. [Risk factors for cardiovascular disease. Results from the Swedish national diabetes register compared with international studies]. *Lakartidningen.* 2013; 110(17-18): 882-885.

24. Gackler D, Jakel S, Fricke L, Reinsch B, Fischer F. [Diabetes and kidneys]. *Deutsche medizinische Wochenschrift.* 2013; 138(18): 949-955.

25. Atabek ME, Ozkul Y, Eklioglu BS, Kurtoglu S, Baykara M. Association between apolipoprotein E polymorphism and subclinic atherosclerosis in patients with type 1

diabetes mellitus. *Journal of clinical research in pediatric endocrinology.* 2012; 4(1): 8-13.

26. Tolonen N, Hietala K, Forsblom C, Harlutsalo V, Makinen VP, Kyto J, Summanen PA, Thorn LM, Waden J, Gordin D, Taskien MR, Groop PH, FinnDiane Study Group. Associations and interactions between lipid profiles, retinopathy and nephropathy in patients with type 1 diabetes. *Journal of internal medicine.* 2013; 274(5): 469-79.

27. Kastelan S, Tomic M, Salopek-Rabatic J, Pavan J, Lukenda A, Gotovac M, Zunec R. The association between the HLA system and retinopathy development in patients with type 1 diabetes mellitus. *Collegium antropologicum.* 2013; 37 Suppl 1: 65-70.

28. Poplawska-Kita A, Siewko K, Krol B, Telejko B, Klimiuk PA, Stokowska W, Gorska M, Szelachowska M. Association between type 1 diabetes and periodontal health. *Adv Med Sci.* 2014; 59(1): 126-31.

29. Al-Sahab B, Ardern CI, Hamadeh MJ, Tamim H. Age at menarche in Canada: results from the National Longitudinal Survey of Children & Youth. *BMC public health.* 2010; 10: 736.

30. Miller RG, Secrest AM, Sharma RK, Songer TJ, Orchard TJ. Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications study cohort. *Diabetes.* 2012; 61(11): 2987-2992.

31. McNally PG, Raymond NT, Burden ML, Burton PR, Botha JL, Swift PG, Burdern AC, Hearnshaw JR. Trends in mortality of childhood-onset insulin-dependent diabetes mellitus in Leicestershire: 1940-1991. *Diabetic medicine.* 1995; 12(11): 961-966.

32. Bas VN, Cetinkaya S, Agladioglu SY, Kendirici HN, Biqili H, Yildirim N, Aycan Z. Insulin oedema in newly diagnosed type 1 diabetes mellitus. *Journal of clinical research in pediatric endocrinology.* 2010; 2(1): 46-48.

33. Bode BW, Sabbah HT, Gross TM, Fredrickson LP, Davidson PC. Diabetes management in the new millennium using insulin pump therapy. *Diabetes/metabolism research and reviews.* 2002; 18 Suppl 1: S14-20.

34. Lawson M, Pacaud, D., Wherrett, D. Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Canadian Journal of Diabetes.* 2008; 34.

35. Newfield RS, Cohen D, Capparelli EV, Shragg P. Rapid weight gain in children soon after diagnosis of type 1 diabetes: is there room for concern? *Pediatric diabetes.* 2009;10(5):310-315.

36. Davis NL, Bursell JD, Evans WD, Warner JT, Gregory JW. Body composition in children with type 1 diabetes in the first year after diagnosis: relationship to glycaemic control and cardiovascular risk. *Archives of disease in childhood.* 2012;97(4):312-315.

37. Purnell JQ, Hokanson JE, Marcovina SM, Steffes MW, Cleary PA, Brunzell JD. Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. Diabetes Control and Complications Trial. *JAMA.* 1998; 280(2): 140-146.

38. Murphy MJ, Metcalf BS, Voss LD, Jeffery AN, Kirkby J, Mallam KM, Wilkin TJ, EarlyBird Study. Girls at five are intrinsically more insulin resistant than boys: The Programming Hypotheses Revisited-The EarlyBird Study. *Pediatrics.* 2004; 113(1): 82-86.

39. Lee IT, Lin SY, Sheu WH. Serial body composition by bioimpedance analysis in a diabetic subject with rapid insulin-induced weight gain--a case report. *The Kaohsiung journal of medical sciences.* 2002; 18(1): 45-48.

40. de Vries L, Bar-Niv M, Lebenthal Y, Tenenbaum A, Shalitin S, Lazer L, Cohen A, Phillip M. Changes in weight and BMI following the diagnosis of type 1 diabetes in children and adolescents. *Acta diabetologica.* 2014; 51(3): 395-402.

41. Smart C, Aslander-van Vliet E, Waldron S. Nutritional management in children and adolescents with diabetes. *Pediatric diabetes.* 2009; 10 Suppl 12: 100-117.

42. Jain V. Management of Type 1 Diabetes in Children and Adolescents. *Indian journal of pediatrics.* 2014; 81(2): 170-2.

43. Adamo KB, Barrowman, N., Colley, R.C., Naylor, PJ., Yaya, S., Harvey, A., Grattan, K.P., and Goldfield, G.S. Activity Begins in Childhood (ABC): a cluster randomized controlled trial to inspire healthy active behaviour in preschoolers. *Trials.* 2014; 15(1): 305.

44. Deshmukh-Taskar P, Nicklas TA, Morales M, Yang SJ, Zakeri I, Berenson GS. Tracking of overweight status from childhood to young adulthood: the Bogalusa Heart Study. *European journal of clinical nutrition.* 2006; 60(1):48-57.

45. Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ. Tracking of childhood overweight into adulthood: a systematic review of the literature. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2008; 9(5): 474-488.

46. Daniels SR. The consequences of childhood overweight and obesity. *The Future of children / Center for the Future of Children, the David and Lucile Packard Foundation.* 2006; 16(1): 47-67.

47. Karnik S, Kanekar A. Childhood obesity: a global public health crisis. *International journal of preventive medicine.* 2012; 3(1):1-7.

48. Sandhu N, Witmans MB, Lemay JF, Crawford S, Jadavji N, Pacaud D. Prevalence of overweight and obesity in children and adolescents with type 1 diabetes mellitus. *Journal of pediatric endocrinology & metabolism : JPEM.* 2008; 21(7): 631-640.

49. EURODIAB ACE Study group. Variation and trends in incidence of childhood diabetes in Europe. EURODIAB ACE Study Group. *Lancet.*2000; 355(9207): 873-6.

50. Diabetes Epidemiology Research International Group. Secular trends in incidence of childhood IDDM in 10 countries. *Diabetes.* 1990; 39(7): 858-864.

51. Nystrom L, Dahlquist G, Rewers M, Wall S. The Swedish childhood diabetes study. An analysis of the temporal variation in diabetes incidence 1978-1987. *Int J Epidemiol.* 1990; 19(1):141-146.

52. Dokheel TM. An epidemic of childhood diabetes in the United States? Evidence from Allegheny County, Pennsylvania. Pittsburgh Diabetes Epidemiology Research Group. *Diabetes care.* 1993; 16(12): 1606-1611.

53. Kostraba JN, Gay EC, Cai Y, Cruickshanks KJ, Rewers MJ, Klingesmith GJ, Chse HP, Hamman RF. Incidence of insulin-dependent diabetes mellitus in Colorado. *Epidemiology (Cambridge, Mass.).* 1992; 3(3): 232-238.

54. Scott RS, Brown LJ, Darlow BA, Forbes LV, Moore MP. Temporal variation in incidence of IDDM in Canterbury, New Zealand. *Diabetes care.* 1992; 15(7): 895-899.

55. LaPorte RE, Orchard TJ, Kuller LH, Wagener DK, Drash AL, Schneider BB, Fishbein HA. The Pittsburgh Insulin Dependent Diabetes Mellitus Registry: the relationship of insulin dependent diabetes mellitus incidence to social class. *American journal of epidemiology.* 1981; 114(3): 379-384.

56. Bruno G, Merletti F, De Salvia A, Lezo A, Arcari R, Pagano G. Comparison of incidence of insulin-dependent diabetes mellitus in children and young adults in the Province of Turin, Italy, 1984-91. Piedmont Study Group for Diabetes Epidemiology. *Diabetic medicine : a journal of the British Diabetic Association.* 1997; 14(11): 964-969.

57. Vehik K, Dabelea D. The changing epidemiology of type 1 diabetes: why is it going through the roof? *Diabetes/metabolism research and reviews.* 2011; 27(1): 3-13.

58. Stanescu DE, Lord K, Lipman TH. The epidemiology of type 1 diabetes in children. *Endocrinology and metabolism clinics of North America.* 2012; 41(4): 679-694.

59. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet.* 2009; 373(9680): 2027-2033.

60. Vehik K, Ajami NJ, Hadley D, Petrosino JF, Burkhardt BR. The Changing Landscape of Type 1 Diabetes: Recent Developments and Future Frontiers. *Current diabetes reports.* 2013; 13(5): 642-50.

61. Vehik K, Hamman RF, Lezotte D, Norris JM, Klingensmith G, Bloch C, Rewers M, Dabelea D. Increasing incidence of type 1 diabetes in 0- to 17-year-old Colorado youth. *Diabetes care.* 2007; 30(3): 503-509.

62. Writing group for the SEARCH for Youth Study Group, Dabelea D, Bell RA, D'Agostino RB, Jr., Imperatore G, Johansen JM, Linder B, Linder B, Liu LL, Loots B, Marcovina S, Mayer-Davis EJ, Pettitt DJ, Waitzfelder B. Incidence of diabetes in youth in the United States. *JAMA .* 2007; 297(24): 2716-24.

63. Karvonen M, Tuomilehto J, Libman I, LaPorte R. A review of the recent epidemiological data on the worldwide incidence of type 1 (insulin-dependent) diabetes mellitus. World Health Organization DIAMOND Project Group. *Diabetologia.* 1993; 36(10): 883-892.

64. Vehik K, Ajami NJ, Hadley D, Petrosino JF, Burkhardt BR. The changing landscape of type 1 diabetes: recent developments and future frontiers. *Current diabetes reports.* 2013; 13(5): 642-650.

65. Porta M. A Dictionary of Epidemiology. New York, NY: *International Epidemiological Association*; 2008.

66. Mayer-Davis EJ, Bell RA, Dabelea D, D'Agostino R Jr, Imperatore G, Lawrence JM, Liu L, Marcovina S. The many faces of diabetes in American youth: type 1 and type 2 diabetes in five race and ethnic populations: the SEARCH for Diabetes in Youth Study. *Diabetes care.* 2009; 32 Suppl 2:S99-101.

67. International Federation of Diabetes. IDF Diabetes Atlas, 4th Edition. 2009.

68. Newhook LA, Penney S, Fiander J, Dowden J. Recent incidence of type 1 diabetes mellitus in children 0-14 years in Newfoundland and Labrador, Canada climbs to over 45/100,000: a retrospective time trend study. *BMC research notes.* 2012; 5: 628.

69. Blanchard JF, Dean H, Anderson K, Wajda A, Ludwig S, Depew N. Incidence and prevalence of diabetes in children aged 0-14 years in Manitoba, Canada, 1985-1993. *Diabetes care.* 1997; 20(4): 512-515.

70. Winnipeg Health Regional Health Authority. Diabetes Education Resource for Children Adolescents: *Annual Report*. 2012.

71. Beaglehole R, Bonita R, Robinson E, Kjellstrom T. The development and evaluation of Basic Epidemiology: Student's Text. *Medical education.* 1992; 26(6): 482-487.

72. Liese AD, D'Agostino RB, Jr., Hamman RF, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics.* 2006; 118(4): 1510-1518.

73. Dart A. The Natural History of Youth Onset Type 2 Diabetes Mellitus. **http://hdl.handle.net/1993/397.** 2010.

74. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature.* 2010; 464(7293): 1293-1300.

75. Skyler JS, Sosenko JM. The evolution of type 1 diabetes. *JAMA : the journal of the American Medical Association.* 2013; 309(23): 2491-2492.

76. Eringsmark Regnell S, Lernmark A. The environment and the origins of islet autoimmunity and Type 1 diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* 2013; 30(2): 155-160.

77. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature.* 2001; 414(6865): 799-806.

78. Diamond J. The double puzzle of diabetes. *Nature.* 2003; 423(6940): 599-602.

79. Soleimanpour SA, Stoffers DA. The pancreatic beta cell and type 1 diabetes: innocent bystander or active participant? *Trends in endocrinology and metabolism: TEM.* 2013; 24(7): 324-331.

80. Atkinson MA. The pathogenesis and natural history of type 1 diabetes. *Cold Spring Harbor perspectives in medicine.* 2012; 2(11).

81. Roche EF, Menon A, Gill D, Hoey H. Clinical presentation of type 1 diabetes. *Pediatric diabetes.* 2005; 6(2): 75-78.

82. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deeb L, Grey M, Anderson B, Holzmeister LA, Clark N, American Diabetes Association. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes care.* 2005; 28(1): 186-212.

83. Pinkey JH, Bingley PJ, Sawtell PA, Dunger DB, Gale EA. Presentation and progress of childhood diabetes mellitus: a prospective population-based study. The Bart's-Oxford Study Group. *Diabetologia.* 1994; 37(1): 70-74.

84. Daneman D. Type 1 diabetes. *Lancet.* 2006; 367(9513): 847-858.

85. Donaghue KC, Chiarelli F, Trotta D, Allgrove J, Dahl-Jorgensen K. Microvascular and macrovascular complications associated with diabetes in children and adolescents. *Pediatric diabetes.* 2009; 10 Suppl 12:195-203.

86. Orchard TJ. From diagnosis and classification to complications and therapy. DCCT. Part II? Diabetes Control and Complications Trial. *Diabetes care.* 1994; 17(4): 326-338.
87. Wolfsdorf J, Glaser N, Sperling MA. Diabetic ketoacidosis in infants, children, and adolescents: A consensus statement from the American Diabetes Association. *Diabetes care.* 2006; 29(5): 1150-1159.

88. Onyiriuka AN, Ifebi E. Ketoacidosis at diagnosis of type 1 diabetes in children and adolescents: frequency and clinical characteristics. *Journal of diabetes and metabolic disorders.* 2013; 12(1): 47.

89. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *The New England journal of medicine.* 2004; 350(22): 2272-2279.

90. Galassetti P, Riddell MC. Exercise and type 1 diabetes (T1DM). *Comprehensive Physiology.* 2013; 3(3): 1309-1336.

91. Marcovecchio ML, Chiarelli F. Microvascular disease in children and adolescents with type 1 diabetes and obesity. *Pediatric nephrology (Berlin, Germany).* 2011; 26(3): 365-375.

92. McVeigh GE, Gibson W, Hamilton PK. Cardiovascular risk in the young type 1 diabetes population with a low 10-year, but high lifetime risk of cardiovascular disease. *Diabetes, obesity & metabolism.* 2013; 15(3): 198-203.

93. Bohme P, Bertin E, Cosson E, Chevalier N. Fear of hypoglycaemia in patients with type 1 diabetes: do patients and diabetologists feel the same way? *Diabetes & metabolism.* 2013; 39(1): 63-70.

94. Evans M, Khunti K, Mamdani M, Galbo-Jorgensen CB, Gundgaard J, Bogelund M, Harris S. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. *Health and quality of life outcomes.* 2013; 11: 90.

95. Avitabile NA, Banka A, Fonseca VA. Glucose control and cardiovascular outcomes in individuals with diabetes mellitus: lessons learned from the megatrials. *Heart failure clinics.* 2012; 8(4): 513-522.

96. Epidemiology of Diabetes Interventions and Complications (EDIC) Study Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA : the journal of the American Medical Association.* 2003; 290(16): 2159-2167.

97. Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. *The Cochrane database of systematic reviews.* 2014; 2: CD009122.

98. Malik FS, Taplin CE. Insulin Therapy in Children and Adolescents with Type 1 Diabetes. *Paediatric drugs.* 2014; 16(2): 141-50.

99. Miles HL, Acerini CL. Insulin analog preparations and their use in children and adolescents with type 1 diabetes mellitus. *Paediatric drugs.* 2008; 10(3): 163-176.

100. Hartman I. Insulin Analogs: Impact on Treatment Success, Satisfaction, Quality of Life, and Adherence. *Clin Med Res.* 2008; 6(2): 54-67.

101. Anderson EJ, Richardson M, Castle G, et al. Nutrition interventions for intensive therapy in the Diabetes Control and Complications Trial. The DCCT Research Group. *Journal of the American Dietetic Association.* 1993; 93(7): 768-772.

102. Purnell JQ, Zinman B, Brunzell JD. The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular disease risk factors and atherosclerosis in type 1 diabetes mellitus: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) study. *Circulation.* 2013; 127(2): 180-187.

103. Conway B, Miller RG, Costacou T, Fried L, Kelsey S, Evans RW, Orchard TJ. Temporal patterns in overweight and obesity in Type 1 diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* 2010; 27(4): 398-404.

104. von Sengbusch S, Muller-Godeffroy E, Hager S, Reintjes R, Hiort O, Wagner V. Mobile diabetes education and care: intervention for children and young people with Type 1 diabetes in rural areas of northern Germany. *Diabetic medicine : a journal of the British Diabetic Association.* 2006; 23(2): 122-127.

105. Svoren BM, Butler D, Levine BS, Anderson BJ, Laffel LM. Reducing acute adverse outcomes in youths with type 1 diabetes: a randomized, controlled trial. *Pediatrics.* 2003; 112(4): 914-922.

106. Brink SJ, Miller M, Moltz KC. Education and multidisciplinary team care concepts for pediatric and adolescent diabetes mellitus. *Journal of pediatric endocrinology & metabolism : JPEM.* 2002; 15(8): 1113-1130.

107. American Diabetes Association. Diabetes management at camps for children with diabetes. *Diabetes care.* 2012; 35 Suppl 1: S72-75.

108. Katamay SW, Esslinger KA, Vigneault M, Johnston JL, Junkins BA, Robbins LG, Sirois IV, Jones-Mclean EM, Kennedy AF, Bush MA, Brule D, Martineau C. Eating well with Canada's Food Guide. development of the food intake pattern. *Nutrition reviews.* 2007; 65(4): 155-166.

109. Nansel TR, Haynie DL, Lipsky LM, Laffel LM, Mehta SN. Multiple indicators of poor diet quality in children and adolescents with type 1 diabetes are associated with higher body mass index percentile but not glycemic control. *Journal of the Academy of Nutrition and Dietetics.* 2012; 112(11): 1728-1735.

110. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes care.* 2008; 31 Suppl 1: S61-78.

111. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public health reports (Washington, D.C. : 1974).* 1985; 100(2): 126-131.

112. Vina J, Sanchis-Gomar F, Martinez-Bello V, Gomez-Cabrera MC. Exercise acts as a drug; the pharmacological benefits of exercise. *British journal of pharmacology.* 2012; 167(1): 1-12.

113. Herbst A, Kordonouri O, Schwab KO, Schmidt F, Holl RW. Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: a multicenter study of 23,251 patients. *Diabetes care.* 2007; 30(8): 2098-2100.

114. Cuenca-Garcia M, Jago R, Shield JP, Burren CP. How does physical activity and fitness influence glycaemic control in young people with Type 1 diabetes? *Diabetic medicine : a journal of the British Diabetic Association.* 2012; 29(10): e369-376.

115. Francescato MP, Carrato S. Management of exercise-induced glycemic imbalances in type 1 diabetes. *Current diabetes reviews.* 2011; 7(4): 253-263.

116. Pihoker C, Forsander G, Wolfsdorf J, Klingensmith GJ. The delivery of ambulatory diabetes care to children and adolescents with diabetes. *Pediatric diabetes.* 2009; 10 Suppl 12: 58-70.

117. Davies M. The reality of glycaemic control in insulin treated diabetes: defining the clinical challenges. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* 2004; 28 Suppl 2: S14-22.

118. Domargard A, Sarnblad S, Kroon M, Karlsson I, Skeppner G, Aman J. Increased prevalence of overweight in adolescent girls with type 1 diabetes mellitus. *Acta paediatrica (Oslo, Norway : 1992).* 1999; 88(11): 1223-1228.

119. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. *Vital and health statistics. Series 11, Data from the national health survey.* 2002; (246): 1-190.

120. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. CDC growth charts: United States. *Advance data.* 2000(314): 1-27.

121. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, Grummer-Strwan LM, Curtin LR, Roche AF, Johnson CL. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics.* 2002; 109(1): 45-60.

122. Frohlich-Reiterer EE, Rosenbauer J, Bechtold-Dalla Pozza S, Hofer SE, Schober E, Holl RW. Predictors of increasing BMI during the course of diabetes in children and adolescents with type 1 diabetes: data from the German/Austrian DPV multicentre survey. *Archives of disease in childhood.* 2014; 99(8): 738-43.

123. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organization technical report series.* 2000; 894: i-xii, 1-253.

124. Power C, Lake JK, Cole TJ. Measurement and long-term health risks of child and adolescent fatness. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* 1997; 21(7): 507-526.

125. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. *Obesity reviews : an official journal of the International Association for the Study of Obesity.*2004; 5 Suppl 1: 4-104.

126. Goran MI. Measurement issues related to studies of childhood obesity: assessment of body composition, body fat distribution, physical activity, and food intake. *Pediatrics.* 1998; 101(3 Pt 2): 505-518.

127. Lahti-Koskia M, Gill, T. Defining Childhood Obesity. *Pediatr Adolesc Med.* 2004; 9: 1-19.

128. Flodmark CE, Lissau I, Moreno LA, Pietrobelli A, Widhalm K. New insights into the field of children and adolescents' obesity: the European perspective. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* 2004; 28(10): 1189-1196.

129. Gray DS, Fujioka K. Use of relative weight and Body Mass Index for the determination of adiposity. *Journal of clinical epidemiology.* 1991; 44(6): 545-550.

130. Taylor RW, Jones IE, Williams SM, Goulding A. Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3-19 y. *The American journal of clinical nutrition.* 2000; 72(2): 490-495.

131. Bellizzi MC, Dietz WH. Workshop on childhood obesity: summary of the discussion. *The American journal of clinical nutrition.* 1999; 70(1): 173S-175S.

132. Weigley ES. Adolphe Quetelet. *The American journal of clinical nutrition.* 2000; 71(3): 853.

133. Himes JH, Dietz WH. Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. The Expert Committee on Clinical Guidelines for Overweight in Adolescent Preventive Services. *The American journal of clinical nutrition.* 1994; 59(2): 307-316.

134. Krebs NF, Jacobson MS. Prevention of pediatric overweight and obesity. *Pediatrics.* 2003; 112(2): 424-430.

135. Cornier MA, Despres JP, Davis N, Grossnilaus DA, Klein S, Lamarche B, Lopez-Jimenez F, Rao G, St-Onge MP, Towfighi A, Poirier P. Assessing adiposity: a scientific statement from the American Heart Association. *Circulation.* 2011; 124(18): 1996-2019.

136. Charbonneau-Roberts G, Saudny-Unterberger H, Kuhnlein HV, Egeland GM. Body mass index may overestimate the prevalence of overweight and obesity among the Inuit. *International journal of circumpolar health.* 2005; 64(2): 163-169.

137. Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. *Arch Intern Med.* 2002; 162(18): 2074-2079.

138. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *The American journal of clinical nutrition.* 2004; 79(3): 379-384.

139. Prentice AM, Jebb SA. Beyond body mass index. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2001; 2(3): 141-147.

140. Carter MA, Dubois L, Tremblay MS, Taljaard M, Jones BL. Trajectories of childhood weight gain: the relative importance of local environment versus individual social and early life factors. *PloS one.* 2012; 7(10): e47065.

141. Himes JH. Challenges of accurately measuring and using BMI and other indicators of obesity in children. *Pediatrics.* 2009; 124 Suppl 1:S3-22.

142. Flegal KM, Ogden CL. Childhood obesity: are we all speaking the same language? *Advances in nutrition (Bethesda, Md.).* 2011; 2(2): 159S-166S.

143. Wang Y, Wang JQ. A comparison of international references for the assessment of child and adolescent overweight and obesity in different populations. *European journal of clinical nutrition.* 2002; 56(10): 973-982.

144. Duncan JS, Duncan EK, Schofield G. Accuracy of body mass index (BMI) thresholds for predicting excess body fat in girls from five ethnicities. *Asia Pacific journal of clinical nutrition.* 2009; 18(3): 404-411.

145. Daniels SR, Khoury PR, Morrison JA. The utility of body mass index as a measure of body fatness in children and adolescents: differences by race and gender. *Pediatrics.* 1997; 99(6): 804-807.

146. Mehta S, Mahajan D, Steinbeck KS, Bermingham MA. Relationship between measures of fatness, lipids and ethnicity in a cohort of adolescent boys. *Annals of nutrition & metabolism.* 2002; 46(5): 192-199.

147. Shields M, Tremblay MS. Canadian childhood obesity estimates based on WHO, IOTF and CDC cut-points. *International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity.* 2010; 5(3): 265-273.

148. Twells LK, Newhook LA. Obesity prevalence estimates in a Canadian regional population of preschool children using variant growth references. *BMC pediatrics.* 2011; 11: 21.

149. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ (Clinical research ed.).* 2000; 320(7244): 1240-1243.

150. World Health Organization. WHO Child Growth Standards based on length/height, weight and age. *Acta paediatrica (Oslo, Norway : 1992). Supplement.* 2006; 450: 76-85.

151. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bulletin of the World Health Organization.*2007; 85(9): 660-667.

152. de Onis M, Blossner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *The American journal of clinical nutrition.* 2010; 92(5): 1257-1264.

153. Flynn MA, McNeil DA, Maloff B, Mutasingwa D, Wu M, Ford C, Tough SC. Reducing obesity and related chronic disease risk in children and youth: a synthesis of evidence with 'best practice' recommendations. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2006; 7 Suppl 1: 7-66.

154. Wang Y, Wu Y, Wilson RF, Bleich S, Cheskin L, Weston C, Showell N, Fawole O, Lau B, Segal J. Childhood Obesity Prevention Programs: Comparative Effectiveness Review and Meta-Analysis*. AHRQ*. 2013; 13: ECH081-EF.

155. World Health Organization. Population-based strategies for prevention of childhood obesity: theory and practice. 2009.

156. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. *The New England journal of medicine.* 2010; 362(6): 485-493.

157. Park MH, Falconer C, Viner RM, Kinra S. The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2012; 13(11): 985-1000.

158. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *International journal of obesity (2005).* 2011; 35(7): 891-898.

159. Kelsey MM, Zaepfel A, Bjornstad P, Nadeau KJ. Age-Related Consequences of Childhood Obesity. *Gerontology.* 2014; 60(3): 222-8.

160. Becton LJ, Shatat IF, Flynn JT. Hypertension and obesity: epidemiology, mechanisms and clinical approach. *Indian journal of pediatrics.* 2012; 79(8): 1056-1061.

161. Chen F, Wang Y, Shan X, Cheng H, Hou D, Zhao X, Wang T, Zhao D, Mi J. Association between childhood obesity and metabolic syndrome: evidence from a large sample of Chinese children and adolescents. *PloS one.* 2012; 7(10): e47380.

162. Silverwood RJ, Pierce M, Hardy R, Thomas C, Ferro C, Sattar N, Kuh D, Nitsch D, National Survey of Health and Development Scientific and Data Collection Teams. Early-Life Overweight Trajectory and CKD in the 1946 British Birth Cohort Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2013; 62(2): 276-284.

163. Lavelle HV, Mackay DF, Pell JP. Systematic review and meta-analysis of school-based interventions to reduce body mass index. *Journal of public health (Oxford, England).* 2012; 34(3): 360-369.

164. Pulgaron ER. Childhood obesity: a review of increased risk for physical and psychological comorbidities. *Clinical therapeutics.* 2013; 35(1): A18-32.

165. Baygi F, Qorbani M, Dorosty AR, et al. Dietary predictors of childhood obesity in a representative sample of children in north east of Iran. *Chinese journal of contemporary pediatrics.* 2013; 15(7): 501-508.

166. Gonzalez A, Boyle MH, Georgiades K, Duncan L, Atkinson LR, MacMillan HL. Childhood and family influences on body mass index in early adulthood: findings from the Ontario Child Health Study. *BMC public health.* 2012; 12: 755.

167. Harrington DW, Elliott SJ. Weighing the importance of neighbourhood: a multilevel exploration of the determinants of overweight and obesity. *Social science & medicine (1982).* 2009; 68(4): 593-600.

168. Willows ND, Hanley AJ, Delormier T. A socioecological framework to understand weight-related issues in Aboriginal children in Canada. *Applied physiology, nutrition, and metabolism* 2012; 37(1): 1-13.

169. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, Uauy R, Martenal and Child Nutrition Study group. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet.* 2013; 382(9890): 427-451.

170. Wang Y, Lim H. The global childhood obesity epidemic and the association between socio-economic status and childhood obesity. *International review of psychiatry (Abingdon, England).* 2012; 24(3): 176-188.

180. Olds T, Maher C, Zumin S, Peneau S, Lioret S, Castetbon K, Bellisle, de Wilde J, Hohepa M, Maddison R, Lissner L, Sjoberg A, Zimmermann M, Aeberil I, Ogden C, Flegal K, Summerbell C. Evidence that the prevalence of childhood overweight is plateauing: data from nine countries. *International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity.* 2011; 6(5-6): 342-360.

181. de Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? *International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity.* 2010; 5(6): 458-460.

182. World Health Organization. Population-baesd approaches to childhood obesity prevention. 2009.

183. Janssen I. The public health burden of obesity in Canada. *Can J Diabetes.* 2013; 37(2): 90-96.

184. Yu BN, Protudjer JL, Anderson K, Fieldhouse P. Weight status and determinants of health in Manitoba children and youth. *Canadian journal of dietetic practice and research : a publication of Dietitians of Canada.* 2010; 71(3): 115-121.

185. Dileepan K, Feldt MM. Type 2 diabetes mellitus in children and adolescents. *Pediatrics in review / American Academy of Pediatrics.* 2013; 34(12): 541-548.

186. Prendergast C, Gidding SS. Cardiovascular risk in children and adolescents with type 2 diabetes mellitus. *Current diabetes reports.* 2014; 14(2): 454.

187. Reinehr T. Type 2 diabetes mellitus in children and adolescents. *World journal of diabetes.* 2013; 4(6): 270-281.

188. Van Name M, Santoro N. Type 2 diabetes mellitus in pediatrics: a new challenge. *World journal of pediatrics : WJP.* 2013; 9(4): 293-299.

189. Knip M, Reunanen A, Virtanen SM, Nuutinen M, Viikari J, Akerblom HK. Does the secular increase in body mass in children contribute to the increasing incidence of type 1 diabetes? *Pediatric diabetes.* 2008; 9(3 Pt 2): 46-49.

190. Verbeeten KC, Elks CE, Daneman D, Ong KK. Association between childhood obesity and subsequent Type 1 diabetes: a systematic review and meta-analysis. *Diabetic medicine : a journal of the British Diabetic Association.* 2011; 28(1): 10-18.

191. Baum JD, Ounsted M, Smith MA. Letter: Weight gain in infancy and subsequent development of diabetes mellitus in childhood. *Lancet.* 1975; 2(7940): 866.

192. Kaminski BM, Klingensmith GJ, Beck RW, Tamborlane WV, Lee J, Hassan K, Schatz D, Kollman C, Redondo MJ, Pediatrics Diabetes Consortium. Body mass index at the time of diagnosis of autoimmune type 1 diabetes in children. *Journal of Pediatrics.* 2013; 162(4): 736-740.

193. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics.* 2007; 120 Suppl 4: S164-192.

194. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocrine reviews.* 2003; 24(5): 668-693.

195. Euling SY, Herman-Giddens ME, Lee PA, Selevan SG, Juul A, Sorensen TI, Dunkel L, Himes JH, Teilmann G, Swan SH. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics.* 2008; 121 Suppl 3: S172-191.

196. De Leonibus C, Marcovecchio ML, Chiavaroli V, de Giorgis T, Chiarelli F, Mohn A. Timing of puberty and physical growth in obese children: a longitudinal study in boys and girls. *Pediatric obesity.* 2014; 9(4): 292-9.

197. Salerno M, Argenziano A, Di Maio S, Gasparini N, Formicola S, De Filippo G, Tenore A. Pubertal growth, sexual maturation, and final height in children with IDDM. Effects of age at onset and metabolic control. *Diabetes care.* 1997; 20(5): 721-724.

198. Dunger D, Ahmed L, Ong K. Growth and body composition in type 1 diabetes mellitus. *Hormone research.* 2002;58 Suppl 1: 66-71.

199. McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. *International journal of obesity.* 2006; 30(4): 598-602.

200. Government of Canada . The Canadian Population in 2011; AGE AND Sex Census. *Statistics Canada.* 2012.

201. Flegal KM, Wei R, Ogden CL, Freedman DS, Johnson CL, Curtin LR. Characterizing extreme values of body mass index-for-age by using the 2000 Centers for Disease Control and Prevention growth charts. *The American journal of clinical nutrition.* 2009; 90(5): 1314-1320.

202. Centres for Disease Control. Cut-offs to define outliers in the 2000 CDC Growth Charts. 2000.

203. Secker D. Promoting optimal monitoring of child growth in Canada: using the new WHO growth charts. *Canadian journal of dietetic practice and research : a publication of Dietitians of Canada.* 2010; 71(1): e1-3.

204. Roberts KC, Shields M, de Groh M, Aziz A, Gilbert JA. Overweight and obesity in children and adolescents: results from the 2009 to 2011 Canadian Health Measures Survey. *Health reports / Statistics Canada, Canadian Centre for Health Information.* 2012; 23(3): 37-41.

205. de Onis M, Garza C, Onyango AW, Borghi E. Comparison of the WHO child growth standards and the CDC 2000 growth charts. *The Journal of nutrition.* 2007; 137(1): 144-148.

206. Schwarz NG, Grobusch MP, Decker ML, Goesch J, Poetschke M, Oyakhirome S, Kombila D, Fortin J, Lell B, Issifou S, Kremsner PG, Klipstein-Grobusch K. WHO 2006 child growth standards: implications for the prevalence of stunting and underweight-for-age in a birth cohort of Gabonese children in comparison to the Centers for Disease Control and Prevention 2000 growth charts and the National Center for Health Statistics 1978 growth references. *Public health nutrition.* 2008; 11(7): 714-719.

207. Government of Manitoba. The weight status of Manitoba Children. 2007.

208. Brownell M DCC, Penfold R, Derksen S, Au W, Schultz J, Dahl M. Manitoba Child Health Atlas Update. 2008.

209. Wilkin TJ. The convergence of type 1 and type 2 diabetes in childhood: the accelerator hypothesis. *Pediatric diabetes.* 2012; 13(4): 334-339.

210. Dabelea D, D'Agostino RB, Jr., Mayer-Davis EJ, Pettitt DJ, Imperatore G, Dolan LM, Hillier TA, Marcovina SM, Linder B, Ruggiero AM, Hamman RF, SEARCH for Diabetes in Youth Study Group. Testing the accelerator hypothesis: body size, beta-cell function, and age at onset of type 1 (autoimmune) diabetes. *Diabetes care.* 2006; 29(2): 290-294.

211. Ahmed ML, Ong KK, Watts AP, Morrell DJ, Preece MA, Dunger DB. Elevated leptin levels are associated with excess gains in fat mass in girls, but not boys, with type 1 diabetes: longitudinal study during adolescence. *The Journal of clinical endocrinology and metabolism.* 2001; 86(3): 1188-1193.

212. Sarnblad S, Ekelund U, Aman J. Dietary fat intake predicts 1-year change in body fat in adolescent girls with type 1 diabetes. *Diabetes care.* 2006; 29(6): 1227-1230.

213. Sarnblad S, Ekelund U, Aman J. Physical activity and energy intake in adolescent girls with Type 1 diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* 2005; 22(7): 893-899.

214. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes care.* 2006; 29(6): 1269-1274.

215. Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu N. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract.* 2004; 66(2): 193-201.

216. van der Baan-Slootweg O, Benninga MA, Beelen A, van der Palen J, Tamminga-Smeulders C, Tijssen JG, van Aalderen WM. Inpatient Treatment of Children and Adolescents With Severe Obesity in the Netherlands: A Randomized Clinical Trial. *JAMA pediatrics.* 2014: 168(9): 807-14.

Appendices

Appendix 1: Letter of approval to access DER-CA database

Health Sciences Centre
Winnipeg

Children's Hospital

Diabetes Education Resource for Children & Adolescents
Phone : (204) 787-3011

January 29, 2013

To whom it my concern,

I am pleased to support Mr. Taru Manyanga's request to access the data found in the electronic database at the Diabetes Education Resource for Children and Adolescents.

Access to this data will be for the purpose of an analysis stemming from a project entitled "Does the increase in BMI associated with initiation of insulin therapy in the 6-12 months after diagnosis with type 1 diabetes among youth age 2-17 predict overweight or obesity at age 18 years?" I understand Mr. Manyanga will be undertaking this project as partial fulfillment of the requirements for a Master's degree in Community Health Sciences, University of Manitoba. His primary supervisor is Dr. Randy Fransoo. Dr. Elizabeth Sellers, a member of our section, is on the thesis committee for this project. All data will be extracted without identifiers and analysis performed in an aggregate fashion only.

I am fully in support of this important project - the results of which may have a positive impact on the health of this population.

Please do not hesitate to contact me if you require any further support or documentation.

Sincerely,

[redacted]
Seth Marks MD MSc FRCPC
Associate Professor, Dept. Pediatrics and Child Health
Head, Section of Pediatric Endocrinology & Metabolism
Medical Director, Diabetes Education Resource for Children and Adolescents.
University of Manitoba

FE307 - 685 William Avenue, Winnipeg, MB R3E 0Z2 / Fax (204) 787-1655 www.hsc.mb.ca

Appendix 2: Letter of approval from Winnipeg Regional Health Authority

Winnipeg Regional Health Authority
Caring for Health

Office régional de la santé de Winnipeg
À l'écoute de notre santé

Research & Evaluation Unit

200-1155 Concordia Ave.
Winnipeg, Manitoba
R2K 2M9 CANADA
TEL: 204| 926.7127
FAX: 204| 947-9970
www.wrha.mb.ca

1155, avenue Concordia, #200
Winnipeg (Manitoba)
R2K 2M9 CANADA
TEL: 204| 926.7127
TELEC: 204| 947-9970
www.wrha.mb.ca

November 29, 2013

Taruwona Manyanga
510 – 72 Donald Street
Winnipeg, MB R3C 1L7

Dear Taruwona:

Re: "Is the Change in BMI After Initiation of Insulin Therapy Among Youth Newly Diagnosed with Type 1 Diabetes Mellitus Associated with Obesity at Age 18?"

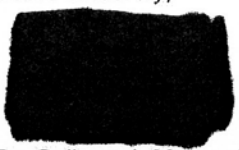
We are pleased to inform you that your request for use/access of WRHA data for the above-named study has been approved by the Winnipeg Regional Health Authority (WRHA) Research Review Committee.

Specifically,

I approve the access and use of the DER-CA data located in the Population Health Research Data Repository housed at MCHP for this project.

We extend best wishes for successful completion of your study.

Yours sincerely,



Dr. Colleen J. Metge, BSc (Pharm), PhD
Director, Research and Evaluation Unit
Chair, WRHA Research Review Committee
Winnipeg Regional Health Authority

cc: Landis Esposito, Chief Privacy Officer, WRHA
Deborah Malazdrewicz, Executive Director, Health Information Management, Manitoba Health
Joy Wei, HIPC Coordinator
Jo-Anne Baribeau, MCHP Repository Access Coordinator

Appendix 3: Health Information Privacy Committee Approval

Manitoba
Health
Health Information Management
4040-300 Carlton Street, Winnipeg, Manitoba, Canada R3B 3M9
T 204-945-7139 F 204-945-1911
www.manitoba.ca

December 16, 2013

Taruwona Manyanga
510-72 Donald Street,
Winnipeg, MB R3C 1L7

File No. 2013/2014 – 49

Dear Taruwona Manyanga,

RE: Is Change in BMI After Initiation of Insulin Therapy Among Youth Diagnosed with Type I Diabetes Mellitus Associated with Obesity at Age 18?

Thank you for submitting the requested documentation for the above named project. The Health Information Privacy Committee has now ***approved*** your request for data for this project.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that *all manuscripts and presentation materials resulting from this study must be submitted for review at least 30 days prior to being submitted for publication or presentation.*

Please note that a Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by MCHP. If you have any questions or concerns, please do not hesitate to contact Joy Wei, Committee Coordinator at 204-786-7204.

Yours truly,

Dr. Biehl, MD, FRCP
Chair, Health Information Privacy Committee

Please quote the file number on all correspondence

c.c. D. Malazdrewicz

Appendix 4: Health Research Ethics Board (HREB) Certificate of Final Approval

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Boards

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Mr. T. Manyanga	UofM / Community Health Sciences	H2013:440

APPROVAL DATE:	EXPIRY DATE:
November 27, 2013	November 27, 2014

STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):
Dr. R. Fransoo

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE;
NA	Is the change in BMI after initiation of insulin therapy among youth newly diagnosed with type 1 diabetes mellitus associated with obesity at age 18?

SPONSORING AGENCIES AND/OR COORDINATING GROUPS:
MHRC

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
November 15, 2013	November 19, 2013

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date

Protocol:

Proposal received November 19, 2013

Consent and Assent Form(s):

Other:

Data Capture Sheet received November 19, 2013

CERTIFICATION

The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION

The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus